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Antagonism of a (+)*N*-Allylnormetazocine Stimulus by (−)PPAP and Several Structurally Related Analogs

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GLENNON, R. A., R. YOUNG AND J. L. HERNDON. *Antagonism of a (+)N-allylnormetazocine stimulus by (−)PPAP and several structurally related analogs.* PHARMACOL BIOCHEM BEHAV **45**(4) 865–869, 1993.—Employing rats trained to discriminate 5 mg/kg of the benzomorphan opioid (+)*N*-allylnormetazocine [(+)NANM] from vehicle, tests of stimulus generalization and antagonism were conducted to determine the influence of several potential σ-receptor ligands. It has been previously suggested that the (+)NANM stimulus may involve concurrent action at σ- and phencyclidine (PCP) receptors. Although the low-affinity σ-antagonist rimcazole was without stimulus-attenuating effect, three novel σ-ligands—(−)PPAP, CNS 3018, and CNS 3093 (ID_{50} doses = 3.2, 6.7, and 4.5 mg/kg, respectively)—antagonized the (+)NANM stimulus in a dose-related fashion. The nonselective serotonergic agent 1-(3-trifluoromethyl)phenylpiperazine (TFMPP) produced partial generalization in (+)NANM-trained animals whereas buspirone, a 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) agonist, attenuated (to 27% drug-appropriate responding) the (+)NANM stimulus. Because the prototypic 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) failed to attenuate the (+)NANM stimulus at pharmacologically relevant doses, it seems unlikely that the (+)NANM stimulus involves a 5-HT_{1A} mechanism. TFMPP and buspirone display modest affinity for σ-receptors and this may account for the present findings with these agents. The present results neither establish a role for σ involvement in the stimulus properties of (+)NANM nor eliminate a role for PCP receptors. They do, however, demonstrate that σ-ligands with little to no affinity for PCP receptors are capable of antagonizing the (+)NANM stimulus.

N-Allylnormetazocine PAPP σ-Receptors Drug discrimination Serotonin

CERTAIN benzomorphan opioids, such as *N*-allylnormetazocine (NANM; SKF10,047), cyclazocine, and pentazocine, although not without affinity for μ, κ, and other opiate receptors, differ sufficiently in their pharmacological actions to qualify their separate categorization as σ-opiates (14). Presently, there is interest in σ-antagonists in that they may represent an entirely novel class of atypical antipsychotic agents that lacks many of the undesirable side effects associated with standard neuroleptic therapy (3,13).

Various opioids serve as discriminative stimuli in animals; their stimulus characteristics are diverse and are generally consistent with mediation by specific receptor types depending upon the agent used as the training drug [reviewed in (10)]. The drug discrimination paradigm has consequently proven useful in understanding and categorizing the stimulus effects of opioids (10). Of particular interest to the present investigation are drug discrimination results obtained with the σ-opiates. Initially, rats trained to discriminate (±)NANM were used to show that its stimulus effects were distinguishable from those of the typical μ-agonist morphine and the κ-agonist ethylketocyclazocine (16). It was later demonstrated that the (+)NANM stimulus generalizes to the σ-ligand *N*-propyl-3-phenylpiperidine [(+)3-PPP], to the PCP/σ ligand phencyclidine (PCP), and to cyclazocine (18,20). However, the (+)NANM stimulus failed to generalize to pentazocine (20), and conflicting results have been obtained with (+)3-PPP [for discussion, see (1,17)]. Other inconsistencies have also been noted. For example, in one investigation the dopamine/σ-ligand haloperidol antagonized the stimulus effects of (+)NANM (20), whereas in two other studies haloperidol was without effect (1,17). In addition, the purported σ-antagonist BMY 14802 failed to antagonize the (+)NANM stimulus and the purported σ-agonist ditolylguanidine (DTG) failed to produce NANM-like stimulus effects (17). In contrast, stimulus generalization occurred to (+)NANM, (+)cyclazocine, and (+)pentazocine in animals trained to discriminate DTG from saline, but haloperidol was without effect in antagonizing the DTG stimulus (11).

Steinfels et al. (18) originally explored the use of (+)NANM as a training drug with the intent that NANM-

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trained animals might serve as an in vivo model of σ-receptor binding. They found, however, that the stimulus properties of drugs are not necessarily predictable from σ-receptor binding and vice versa. The involvement of σ- and PCP receptors in the mediation of the stimulus effects of NANM remains unclear. It appears that the (+)NANM stimulus may be mediated by multiple mechanisms involving σ- and PCP (and perhaps other ?) receptors. Steinfels and coworkers suggested that the stimulus involves concurrent actions at both σ *and* PCP sites (20), whereas Singh et al. (17) concluded that (+)NANM produces a compound stimulus in which the σ component plays only a minor role. The latter investigators further suggested that the results of their investigations are consistent with a mechanism involving the NMDA receptor complex (17). In a most recent attempt to explain some of the previously published inconsistencies, Picker (15) investigated the stimulus effects of multiple training doses of (+)- and (−)NANM and concluded that the stimulus effects of (+)NANM involve both a PCP and σ component.

1-[(3-Trifluoromethyl)phenyl]piperazine (TFMPP) is a serotonergic agent that binds at several populations of 5-hydroxytryptamine (5-HT) receptors (9). TFMPP serves as a discriminative stimulus in animals, and although there is no evidence supporting involvement of a 5-HT_{1A} serotonergic mechanism (10) the TFMPP stimulus can be attenuated by pretreatment of animals with the 5-HT_{1A} agonist buspirone (9). Attempts were made to find a reasonable explanation for the attenuating effect of buspirone. Because both TFMPP and buspirone bind with modest affinity at σ-receptors (9,12), the possibility was raised that the mechanism underlying the TFMPP stimulus might involve, at least in part, an NANM-like (or σ) component; indeed, the TFMPP stimulus was shown to generalize to (+)NANM (9). Thus, in the present study it was of interest to determine a) if a (+)NANM stimulus would generalize to TFMPP and b) if the (+)NANM stimulus could be attenuated by buspirone. In addition, we recently developed several novel σ-ligands and it was also of interest to determine whether one of these agents could influence the (+)NANM stimulus. The low-affinity putative σ-antagonist rimcazole was also examined for the purpose of comparison.

METHOD

Drug Discrimination Studies

Subjects were five male Sprague-Dawley rats weighing 250–300 g at the start of the study. Animals were first trained to lever-press for sweetened milk reward using standard two-lever operant chambers (Coulbourn Instruments Model E10-10) housed within sound- and light-attenuating outer chambers. Once lever-pressing behavior was acquired, animals were trained to discriminate IP injections of (+)NANM (5.0 mg/kg) from 0.9% sterile saline (1.0 ml/kg), that is, rats were trained to respond on a variable-interval 15-s (VI 15) schedule of reinforcement; once rates of responding stabilized, animals received an injection of drug or saline 15 min prior to each session. Drug or saline was administered on a double-alternation schedule (i.e., 2 days drug, 2 days saline) and training sessions were of 15 min duration. For approximately half the animals, the right lever was designated the drug-appropriate lever and the left the vehicle-appropriate lever; the situation was reversed for the remaining animals, that is, animals' responses were reinforced with sweetened milk when the appropriate behavior was elicited. On every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) period followed by a 12.5-min training session. Data collected during the extinction period included percent drug-appropriate lever responding (i.e., the number of responses on the drug-designated lever/total number of responses, expressed as a percent), and total responses made during the 2.5-min session (expressed as responses/min).

Once rats consistently (i.e., for 3 consecutive weeks) made > 80% of their responses on the drug-appropriate lever after administration of drug and < 20% of their responses on the same lever after injection of saline, stimulus generalization and antagonism studies were begun. During these investigations, test sessions were interposed among the training sessions; however, after the 2.5-min extinction period animals were returned to their home cages. During antagonism tests, rats were injected with purported antagonists 15 min prior to administration of 5.0 mg/kg (+)NANM. Stimulus antagonism was said to have occurred when animals made ≤ 20% of their responses on the drug-appropriate lever. ID_{50} (inhibition dose 50%) values were calculated by the method of Finney (4). During generalization tests, rats were injected with doses of a substitute compound and, 30 min later (15 min for TFMPP), tested under extinction conditions. Stimulus generalization was said to have occurred when animals made ≥ 80% of their responses on the drug-appropriate lever.

Drugs

R(−)*N*-3-Phenyl-*n*-propyl-1-phenyl-2-aminopropane HCl [(−)PPAP] (5), *N*-3-phenyl-*n*-propyl-1-(4-hydroxyphenyl)-2-aminopropane HCl (CNS 3018) (7), and or *N*-cyclohexylmethyl-*N*-[5-(phenyl)pentyl]amine HCl (CNS 3093) (2) were previously synthesized in our laboratories. TFMPP HCl and 8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT) were purchased from Research Biochemicals, Inc. (Natick, MA). (+)*N*-Allylnormetazocine HCl was a gift from NIDA (Bethesda, MD) and buspirone HCl was obtained from Dr. J. Rosecrans (MCV/VCU). Rimcazole HCl was a gift from the Burroughs Wellcome Co. (Research Triangle Park, NC). All solutions were prepared fresh daily in sterile saline and administered in a 1-ml/kg injection volume except (−)PPAP and CNS 3018, which were administered in a 2-ml/kg injection volume. All injections were via the IP route.

RESULTS

Animals were trained to discriminate 5 mg/kg (+)NANM from saline such that they made > 80% of their responses on the drug-appropriate lever when administered the training dose of (+)NANM (Table 1). Administration of vehicle (0.9% saline, 1.0 ml/kg) elicited < 10% drug-appropriate responding.

Tests of stimulus generalization were conducted with (+)NANM, TFMPP, (−)PPAP, CNS 3018, and CNS 3093 (Table 1). At doses of 0.1 and 0.5 mg/kg, TFMPP produced vehicle-appropriate responding. At a TFMPP dose of 0.7 mg/kg, only two animals responded (58% NANM-appropriate responding); higher doses of TFMPP resulted in disruption of behavior. At all doses tested, (−)PPAP, CNS 3018, and CNS 3093 produced no more than 11% drug-appropriate responding. A single dose of buspirone was examined in a test of stimulus generalization; at 2.0 mg/kg (data not shown), buspirone elicited 10 (± 2)% drug-appropriate responding in five animals (response rate = 8.8 ± 1.6 responses/min).

Tests of stimulus antagonism were conducted by administration of doses of buspirone, 8-OH-DPAT, rimcazole,

TABLE 1

RESULTS OF STIMULUS GENERALIZATION AND ANTAGONISM STUDIES WITH RATS TRAINED TO DISCRIMINATE 5 mg/kg (+)NANM FROM VEHICLE

Treatment	Dose (mg/kg)	n*	% (+)NANM-Appropriate Responding†	Response Rate (responses/min)‡
(+)NANM	1.25	5/5	12 (± 5)	11.0 (±1.7)
	2.5	5/5	48 (±18)	10.8 (±2.5)
	5.0	5/5	93 (± 5)	12.5 (±1.9)
Saline (0.9%) 1 ml/kg		5/5	6 (± 3)	10.3 (±2.1)
TFMPP	0.1	4/4	6 (± 3)	11.7 (±1.9)
	0.5	4/4	13 (± 9)	4.3 (±0.5)
	0.7	2/4	58 (±16)	4.0 (±1.2)
	0.8	1/4	§	
	1.0	1/4	§	
Buspirone + NANM (5.0)	1.2	4/5	67 (±18)	11.0 (±7.3)
	1.6	3/3	29 (±21)	4.3 (±0.9)
	2.0	4/5	27 (± 7)	7.7 (±2.0)
	2.2	0/5	§	
	2.4	0/4	§	
8-OH-DPAT + NANM (5.0)	0.01	4/4	89 (± 3)	21.0 (±8.0)
	0.07	3/5	85 (± 5)	6.0 (±0.4)
	0.15	0/5	§	
Rimcazole + NANM (5.0)	5.0	5/5	91 (± 6)	14.2 (±1.7)
	10.0	5/5	77 (±11)	13.4 (±2.1)
	13.5	3/5	74 (± 7)	6.1 (±1.8)
	15.0	1/5	§	
	20.0	0/5	§	
(−)PPAP	1.0	4/4	5 (± 3)	9.8 (±1.8)
	5.0	4/4	6 (± 5)	11.1 (±1.9)
	10.0	4/4	8 (± 8)	7.8 (±2.6)
(−)PAPP + NANM (5.0)	1.0	4/4	81 (±12)	11.1 (±3.0)
	5.0	4/4	39 (±16)	13.2 (±1.0)
	10.0	4/4	19 (± 9)	11.4 (±4.0)
	ID_{50} = 3.2 (1.1–9.5) mg/kg¶			
CNS 3018	2.5	4/4	11 (± 6)	9.8 (±2.7)
	5.0	4/4	6 (± 3)	11.8 (±3.1)
	10.0	4/4	9 (± 3)	11.6 (±2.1)
CNS 3018 + NANM (5.0)	5.0	4/4	79 (±10)	14.6 (±3.2)
	6.25	4/4	54 (±12)	11.8 (±2.3)
	7.5	4/4	34 (±22)	15.1 (±1.9)
	10.0	4/4	20 (± 9)	9.7 (±1.7)
	ID_{50} = 6.7 (5.1–9.1) mg/kg¶			
CNS 3093	3.0	3/4	8 (± 2)	10.6 (±2.0)
	6.5	3/3	1 (± 1)	14.8 (±5.3)
CNS 3093 + NANM (5.0)	3.0	4/4	72 (±19)	13.6 (±3.1)
	6.0	3/3	49 (±29)	3.7 (±1.1)
	6.5	4/4	18 (± 9)	8.4 (±3.6)
	7.0	1/4	§	
	8.0	1/5	§	
	ID_{50} = 4.5 (2.7–7.7) mg/kg¶			

*Number of animals responding/number treated.

†Percent of total responses on the (+)NANM-designated lever; data collected during 2.5-min extinction session.

‡Data collected during 2.5-min extinction session.

§Disruption of behavior (i.e., majority of animals failed to make >5 total responses during the 2.5-min extinction session).

¶ID_{50} value followed in parentheses by 95% confidence limits.

(−)PPAP, CNS 3018, and CNS 3093 in combination with the training dose of (+)NANM. (+)NANM in combination with 1.2, 1.6, and 2.0 mg/kg buspirone resulted in 67, 29, and 27% drug-appropriate responding, respectively; 2.2 and 2.4 mg/kg buspirone resulted in disruption of behavior (Table 1). Doses of 0.01 and 0.07 mg/kg 8-OH-DPAT failed to antagonize the (+)NANM stimulus; 0.15 mg/kg 8-OH-DPAT plus 5 mg/kg (+)NANM produced disruption of behavior.

Rimcazole failed to antagonize the (+)NANM stimulus at doses of up to 13.5 mg/kg; administration of higher doses of rimcazole in combination with the training dose of (+)NANM resulted in disruption of behavior. (−)PPAP and CNS 3018 antagonized the (+)NANM stimulus (ID_{50} values = 3.2 and 6.7 mg/kg, respectively) with little effect on response rates. CNS 3093 also antagonized the (+)NANM stimulus (ID_{50} value = 4.5 mg/kg); however, doses producing antagonism resulted in depressed response rates.

DISCUSSION

TFMPP stimulus generalization has been shown to occur to (+)NANM (9); at the dose of TFMPP (i.e., 13 mg/kg) where generalization occurred, animals were severely disrupted as evidenced by their low rates of responding. In the present study, the (+)NANM stimulus failed to generalize to TFMPP. However, doses of TFMPP > 0.1 mg/kg resulted in depressed rates of responding or disruption of behavior. As a result, the present findings with TFMPP are inconclusive.

On the other hand, buspirone does seem able to attenuate the (+)NANM stimulus. However, as with the TFMPP stimulus (10), buspirone did not completely antagonize the (+)NANM stimulus (Table 1). Although it has been previously shown, by the use of relatively nonselective serotonin agonists and antagonists, that the NANM stimulus does not involve a serotonergic mechanism (19), buspirone is noted for its activity as a 5-HT_{1A} agonist. Consequently, we explored the possibility that another 5-HT_{1A} agonist might also antagonize the (+)NANM stimulus. As shown in Table 1, however, the prototypic 5-HT_{1A} antagonist 8-OH-DPAT had no significant effect on percent drug-appropriate responding up to a dose that resulted in disruption of behavior. The present results with buspirone do not exclude the possibility that it may possess some activity as an NANM antagonist.

Rimcazole is reported to be a competitive σ-receptor antagonist (3). In the present investigation, rimcazole failed to antagonize the (+)NANM stimulus at doses of up to 13.5 mg/kg; doses of 15 and 20 mg/kg disrupted animals' behavior. Because rimcazole binds at σ-receptors only with low affinity (IC_{50} = 1,640 nM) (13), it is possible that antagonism might have been observed at higher doses had disruption of behavior not occurred.

(−)PPAP (σ K_i = 23 nM) (7) produced less than 10% (+)NANM-appropriate responding at doses of 1–10 mg/kg (Table 1). However, when administered in combination with the training dose of (+)NANM (5 mg/kg) (−)PPAP antagonized the (+)NANM stimulus in a dose-related fashion (ID_{50} = 3.2 mg/kg). Shortly after these results were obtained, it was found that (−)PPAP displays only a fourfold selectivity for σ vs. 5-HT_{1A} receptors (6). Because buspirone also binds at 5-HT_{1A} receptors, we evaluated the 5-HT_{1A} ligand 8-OH-DPAT (vide supra) and two analogs of (−)PPAP with greater σ vs. 5-HT_{1A} selectivity. CNS 3018 and CNS 3093 (σ K_i = 10.4 and 1.2 nM, respectively) (2,7) bind with approximately 60- and 600-fold selectivity for σ vs. 5-HT_{1A} receptors (5-HT_{1A} IC_{50} = 590 and 600 nM, respectively) (J. B. Fischer, unpublished data). As with (−)PPAP, neither agent produced greater than 11% (+)NANM-appropriate responding (Table 1) and both agents antagonized the (+)NANM stimulus when administered in combination with 5 mg/kg (+)NANM (ID_{50} = 6.7 and 4.5 mg/kg).

(−)PPAP and its derivatives antagonized the (+)NANM stimulus (Table 1); as such, they may be termed (+)NANM antagonists. This does not necessarily imply that they are σ-receptor antagonists. It has been suggested that (+)NANM produces a compound stimulus involving both (15), and perhaps concurrent (20) actions at, σ and PCP sites. If this is the case, agents capable of interfering with a portion of this stimulus mechanism (e.g., the σ component) may act as (+)NANM-stimulus antagonists. Clearly, (−)PPAP displays little affinity for PCP receptors (IC_{50} > 75,000 nM) (5); thus, it is unlikely to interfere directly with a PCP receptor mechanism. On the other hand, (−)PPAP binds at σ-receptors and may act as a σ-antagonist.

The binding profiles of (−)PPAP-related compounds have been examined and these agents typically show low affinity for most neurotransmitter receptors (7). (−)PPAP, for example, displays little affinity (K_i > 10,000 nM) for D_1 dopamine, adrenergic, kainate, quisqualate, 5-HT_{1B-1D}, 5-HT_3, and benzodiazepine receptors [(8) and J. B. Fischer, unpublished data]. Although there is no evidence for mediation of the (+)NANM stimulus by a dopaminergic mechanism (19,20), the stimulus has been antagonized by haloperidol (20). (−)PPAP binds with low affinity (IC_{50} > 5,000 nM) at D_2 dopamine receptors (5). It would appear unlikely that the (+)NANM stimulus is mediated by one of these mechanisms.

SUMMARY

The stimulus generalization study with TFMPP was inconclusive. The (+)NANM stimulus did not generalize to TFMPP; rather, partial generalization was observed and, at higher doses of TFMPP, animals' behavior was disrupted. However, as previously demonstrated using TFMPP-trained animals (9), buspirone partially antagonized the (+)NANM stimulus (Table 1). Although buspirone is a 5-HT_{1A} agonist, the prototypic 5-HT_{1A} agonist 8-OH-DPAT failed to antagonize the (+)NANM stimulus. Although pharmacologically relevant doses were used, even a dose of 0.15 mg/kg 8-OH-DPAT administered in combination with the training dose of (+)NANM resulted in disruption of behavior. Here too, then, the results are somewhat inconclusive. Buspirone binds with modest affinity at σ-receptors and it has been suggested that buspirone's antagonism of a TFMPP stimulus might involve a σ mechanism (9). The σ-antagonist rimcazole failed to antagonize the (+)NANM stimulus at the doses evaluated, but this may be due to its low affinity for σ-receptors. However, (−)PPAP, CNS 3018, and CNS 3093 all antagonized the (+)NANM stimulus in a dose-related fashion. Although (−)PPAP shows little selectivity for σ vs. 5-HT_{1A} receptors, the latter two agents bind at σ sites with 60- and 600-fold selectivity, respectively. Further, these compounds display little affinity for PCP sites. Thus, although the (+)NANM stimulus may involve multiple mechanistic components agents with affinity for σ-receptors, yet lacking significant affinity for PCP and dopamine receptors, are able to antagonize the (+)NANM stimulus.

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