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Discriminative Stimulus Properties of NIK-247 and Tetrahydroaminoacridine, Centrally Active Cholinesterase Inhibitors, in Rats

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YAMAMOTO, T., M. OHNO, K. SUGIMACHI AND S. UEKI. *Discriminative stimulus properties of NIK-247 and tetrahydroaminoacridine, centrally active cholinesterase inhibitors, in rats.* PHARMACOL BIOCHEM BEHAV **44**(4) 769–775, 1993. – The discriminative stimulus effect of the novel centrally active cholinesterase inhibitor, NIK-247, was investigated in rats and compared with that of tetrahydroaminoacridine (THA). Rats were trained to discriminate either 10 mg/kg NIK-247 or 1.8 mg/kg THA from saline in a two-lever food-reinforced procedure. The stimulus effect of NIK-247 was substituted for by the cholinesterase inhibitors, THA and physostigmine. The THA stimulus was substituted for by NIK-247 and physostigmine. The muscarinic receptor agonist arecoline substituted for the NIK-247 and THA stimuli. Both stimulus effects of NIK-247 and THA were blocked by the muscarinic antagonist scopolamine. The dopaminergic-activating drugs amantadine and lisuride substituted for the stimulus effects of NIK-247 and THA. However, neither the NIK-247 nor the THA stimulus was antagonized by the dopamine antagonists haloperidol, SCH 23390, and sulpiride. These results suggest that the discriminative stimulus effects of NIK-247 and THA are mediated by muscarinic receptors, and that the dopaminergic activity resulting from cholinergic activation may account for some part of both stimuli.

Drug discrimination Cholinesterase inhibitor NIK-247 Tetrahydroaminoacridine (THA)
Muscarinic receptor Rat

THE most striking and consistent change that occurs in Alzheimer's disease (AD) is in the central cholinergic system, as measured by marked reductions in choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity in the hippocampus and cortex (5,8). The importance of the cholinergic system as a possible site for treatment of dementia is underlined by the finding that the degree of cholinergic deficits correlates with the severity of cognitive impairments in patients with AD (24). The use of AChE inhibitors is a pharmacological strategy for restoring cholinergic function in AD brains. Summers et al. (30,31) have reported that tetrahydroaminoacridine (THA), a centrally acting AChE inhibitor, was effective in the restoration of memory deficits in AD patients. However, since THA is toxic to liver cells, its clinical utility has not been substantiated (4). NIK-247 [9-amino-2,3,5,6,7,8-hexahydro-1H-cyclopenta-(b)-quinoline monohydrate hydrochloride], synthesized as a structural analogue of THA, also has inhibitory effects on AChE activity in the brain (11,28) and has been shown to improve memory impairments in several animal models of dementia (17,33). We have also previously demonstrated, using a three-panel runway task, that NIK-247, as well as THA, alleviated memory deficits induced by scopolamine and hippocampal lesions (35).

The drug discrimination paradigm has been one of the most widely used tools in behavioral pharmacology (29) and research based on this paradigm has made important contributions to our knowledge of the mode of action of direct cholinergic agonists and antagonists (13,16,22,26). With regard to AChE inhibitors, Johansson and Järbe (12) and Overton (23) have reported that physostigmine can serve as a discriminative stimulus cue in a T-maze shock-escape procedure. Recently, several investigators have extended the analysis of the stimulus effects of physostigmine, using a two-lever food-reinforced procedure and a two-choice, discrete-trial avoidance paradigm (14,15,32). The results of these experiments suggest that the discriminative stimulus effects of physostigmine are mediated by central muscarinic receptors. However, to date, there have been no reports of the discriminative stimulus properties of AChE inhibitors other than physostigmine. Accordingly, we carried out this study to clarify the discriminative characteristics of two centrally acting cholinesterase inhibitors, NIK-247 and THA, in rats.

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METHOD

Animals

Eight- to ten-week-old male rats of the Wistar strain (Nippon SLC) were used. The rats weighed 230–250 g at the start of the experiment, and then they were placed on a deprivation schedule to maintain their weights at approximately 80% of the free-feeding level, supplemented for normal growth. The rats were housed in groups of four per cage with water freely available. Room temperature was kept at 23 ± 2°C, with a 12L : 12D cycle (light period: 07:00–19:00 h) maintained throughout the experiment.

Apparatus

Eight standard operant chambers, each equipped with two levers (Gerbrands: 30.5 × 23.5 × 26.5 cm) were used. The levers were placed 17 cm apart, at a height of 5.5 cm above the floor grid, and a feeder was mounted between the levers. A food pellet (about 50 mg) was delivered by a pellet dispenser. Scheduling of experimental contingencies and data collection were accomplished with a microcomputer (NEC, PC-8801mkII) connected to the chambers through solid-state programming equipment (Muromachi Kikai).

Discrimination Training

With food as a positive reinforcer, rats were trained to press either one of the two levers on a fixed-ratio one (FR 1) schedule, and their behavior was shaped progressively until 10 consecutive lever-press responses were required to obtain the reinforcer (FR 10). When all the rats responded reliably according to this schedule (approximately 40–50 responses/min), they were divided into two groups. The left lever was assigned as the drug lever for half of the rats and the right lever served this purpose for the other half, to counteract the possible effect of lever preference. When the drug was administered, 10 consecutive responses on one lever (drug lever) were followed by food delivery, whereas 10 consecutive responses on the other lever (saline lever) resulted in food delivery when saline was administered. The rats were placed in the chamber immediately after injection, and sessions did not start until houselights were turned on 30 min after injection. Fourteen rats were trained to press the drug lever after they received an IP injection of NIK-247 and to press the saline lever after an injection of saline (designated NIK-247-trained rats). As described in the Results section, the initial training dose of 3.2 mg/kg NIK-247 was increased to 5.6 mg/kg at the 81st training session. At the 101st session, the training dose of NIK-247 was further increased to 10 mg/kg, and the dose then remained at this level throughout the subsequent experiment. Discrimination training after alternating administration of NIK-247 or saline was conducted once each day. Each session was terminated after 30 min or 50 food reinforcements, whichever occurred earlier. Sessions were run on 6 days per week, and generally, drug and saline injections alternated from one training day to the next. After rats consistently responded with less than 10 incorrect lever-pressings, they were subjected to a further stage of training with four sequential sessions of coupled alternation (saline, saline, drug, drug). These conditions remained in effect until the rats responded with less than 10 incorrect lever-pressings, over six consecutive sessions. Following this, we determined whether NIK-247 and saline were correctly discriminated, using a test schedule in which responding on either lever was reinforced. The discrimination criterion was two consecutive test probes (drug- and saline-test) with 80% or more appropriate-lever responses. If a rat failed to meet this criterion, additional training sessions were given until it did meet the criterion.

In the same way, the other group of 13 rats was trained to discriminate an IP injection of THA from saline injection (designated THA-trained rats), with the exception of the training dose. At the 61st training session, the initial training dose of 1 mg/kg THA was increased to 1.8 mg/kg, and it remained at this level throughout the subsequent experiment.

Discrimination Testing

These testing procedures were identical to the training procedures outlined above, except that 10 consecutive responses on either of the two levers produced food reinforcement. A test session was continued until 50 reinforcements had been obtained or until 30 min had elapsed. Once the discrimination criterion was met, dose–effect determinations were conducted for each training drug. The substitution test was run 30 min after animals received an IP injection of a test drug. In the antagonism test, the rats were treated with the antagonists 10 min before the training dose of each drug was injected, the training dose being injected 30 min prior to the test session. These tests for various drugs were conducted on a random basis, with the restriction being that the same animal was used to study the different doses of each test drug.

Data Analysis

Data present the mean percentage of responses on the drug-appropriate lever during the entire test session. Animals showing less than 50 responses during the test session were not included in the calculations for the mean percentage of drug-appropriate responses. The response rate was calculated as the mean total number of responses divided by the number of minutes taken for the session. Variability was expressed as the SE. A test drug was considered to produce discriminative stimulus effects similar to those of the training drug (10 mg/kg NIK-247 or 1.8 mg/kg THA) if at least 80% of the responses were made on the drug-appropriate lever.

Drugs

The drugs used in this study were NIK-247 [9-amino-2,3,5,6,7,8-hexahydro-1H-cyclopenta-(b)-quinoline monohydrate hydrochloride; Nikken Chemical Co. Ltd., Tokyo, Japan), tetrahydroaminoacridine hydrochloride (THA; Aldrich Chemical Co., Inc., Milwaukee, WI), physostigmine salicylate (Sigma Chemical Co., St. Louis, MO), (-)scopolamine hydrobromide (Sigma), arecoline hydrobromide (Sigma), amantadine hydrochloride (CIBA-GEIGY, Basel, Switzerland), lisuride hydrogen maleate (Nihon Schering, Osaka, Japan), dextrorphan hydrochloride (Nippon Roche), phencyclidine hydrochloride, calcium hopantenate (Tanabe Seiyaku Co., Ltd., Osaka, Japan), haloperidol (Serenace Injection, Dainippon Pharmaceutical Co., Ltd., Osaka, Japan), SCH 23390 maleate (Schering) and sulpiride (Dogmatyl Injection, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan). Haloperidol and sulpiride injections were diluted with appropriate amounts of distilled water and all the other drugs were dissolved in distilled water. Drug doses have been expressed in terms of the salt. Drugs were administered intraperitoneally in a volume of 0.1 ml per 100 g body weight.

RESULTS

Although the rats had been trained to discriminate between 3.2 mg/kg NIK-247 and saline in 80 sessions, they did not

learn to discriminate NIK-247 from saline, and then the training dose was increased to 5.6 mg/kg. Even after the rats were given 20 training sessions with 5.6 mg/kg NIK-247, they did not achieve a stable discriminative performance. Thus, the training dose of NIK-247 was finally increased to 10 mg/kg at the 101st session. Thereafter, the rats required approximately 15 sessions to discriminate 10 mg/kg NIK-247 from saline and to meet the criterion of selecting the correct lever. Three of the 14 rats in this group failed to discriminate between 10 mg/kg NIK-247 and saline, and they were eliminated from the study. With regard to THA, initial training began at a dose of 1 mg/kg. After 60 training sessions were given, the rats had not achieved stable discriminative performance. The training dose of THA was then increased to 1.8 mg/kg at the 61st session. About 44 sessions were required for the rats to discriminate THA from saline after training with 1.8 mg/kg THA began. One of the 13 rats failed to meet the criterion of correct lever selection in the THA-saline discrimination. Once the discrimination had been established, it was well-maintained thereafter, with stable appropriate lever-pressing responses in both the NIK-247- and THA-trained rats. Training doses of 10 mg/kg NIK-247 and 1.8 mg/kg THA were continued for all rats for the subsequent experiment.

Dose-effect determinations for NIK-247 showed that the percentage of drug-appropriate responses in the 10 mg/kg NIK-247-trained rats increased with the dose of NIK-247 (Fig. 1). NIK-247 reduced the response rate in a dose-dependent manner. THA produced a dose-related increase in the percentage of drug-appropriate responses and a reduction in the response rate in the NIK-247-trained rats. A dose of 3.2 mg/kg of THA substituted for the stimulus effect of 10 mg/kg NIK-247 [drug-appropriate responses (mean ± SE): 84.3 ± 13.6%]. Physostigmine and arecoline caused dose-dependent increases in the percentage of NIK-247-appropriate responses without affecting the response rate. Doses of 0.32 mg/kg of physostigmine and 18 mg/kg of arecoline produced discriminative stimuli similar to those of 10 mg/kg NIK-247 (82.7 ± 16.5% and 83.3 ± 16.1%, respectively).

The percentage of drug-appropriate responses in the 1.8 mg/kg THA-trained rats increased with the dose of THA (Fig. 2). NIK-247 and physostigmine also produced dose-related increases in the percentage of drug-appropriate responses in the 1.8 mg/kg THA-trained rats. Doses of 10 mg/kg of NIK-247 and 0.56 mg/kg of physostigmine substituted for the stimulus effect of 1.8 mg/kg THA (86.6 ± 10.9% and 82.6 ± 16.5%, respectively). Arecoline produced THA-appropriate responses, and its maximal value was 71.1 ± 18.1% at the 10 mg/kg dose. Whereas only one of eight rats given 10 mg/kg arecoline showed suppression of the lever-pressing response (less than 50 responses during the entire test session), five of seven rats exhibited a substitution for the THA stimulus. The higher dose of 18 mg/kg arecoline caused suppression of lever-pressing in two of eight rats.

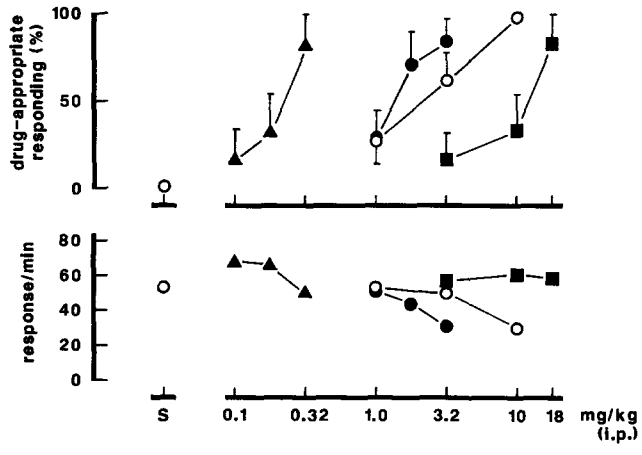

FIG. 1. Percentage of drug-appropriate responses and response rate after the administration of NIK-247 (○), THA (●), physostigmine (▲), and arecoline (■) to rats trained to discriminate 10 mg/kg NIK-247 from saline. Drugs were given 30 min before the substitution test. Each point represents the mean ± SE in each group of 6–11 animals.

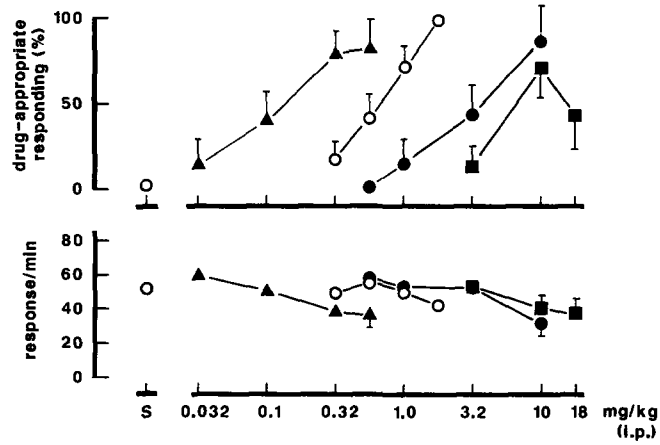

FIG. 2. Percentage of drug-appropriate responses and response rate after the administration of THA (○), NIK-247 (●), physostigmine (▲), and arecoline (■) to rats trained to discriminate 1.8 mg/kg THA from saline. Drugs were given 30 min before the substitution test. Each point represents the mean ± SE in each group of 5–12 animals.

Table 1 shows the effects of drugs other than cholinergic compounds on the percentage of drug-appropriate responses and the response rate in the 10 mg/kg NIK-247-trained rats. Amantadine and lisuride dose-dependently increased the NIK-247-appropriate responses and substituted for the NIK-247 stimulus at 32 and 0.32 mg/kg, respectively. Across the range of doses evaluated, calcium hopantenate and dextrorphan produced only intermediate levels of drug-appropriate responses along with a reduction in the response rate in the NIK-247-trained rats. Phencyclidine, at doses up to 3.2 mg/kg, did not produce a substitution for the NIK-247 stimulus. A higher dose of phencyclidine, 10 mg/kg, caused suppression of the lever-pressing in three of five rats (data not shown). In the THA-trained rats, lisuride produced a significant increase in drug-appropriate responses, and 0.1 mg/kg of lisuride substituted for the THA stimulus, whereas amantadine, at doses up to 32 mg/kg, induced only intermediate levels of THA-appropriate responses (Table 2). Calcium hopantenate at 1000 mg/kg completely substituted for the THA stimulus and substantially reduced the response rate. Four of seven rats given 1000 mg/kg of calcium hopantenate exhibited suppression of lever-pressing responses and the three other rats showed THA-appropriate responses. Although dextrorphan at 10 and 32 mg/kg also produced a partial substitution for the THA stimulus, phencyclidine, at doses up to 3.2 mg/kg, did not produce drug-appropriate responses in the THA-trained rats. A dose of 3.2 mg/kg of phencyclidine caused suppression of lever-pressing in two of six rats.

TABLE 1

EFFECTS OF AMANTADINE, LISURIDE, DEXTRORPHAN, PHENCYCLIDINE, AND CALCIUM HOPANTENATE ON PERCENTAGE OF DRUG-APPROPRIATE RESPONSES AND RESPONSE RATE IN RATS TRAINED TO DISCRIMINATE 10 mg/kg NIK-247 FROM SALINE

Compound	mg/kg (IP)	% Responses on drug-lever	R/N	D/R	Responses/min
Saline	–	1 ± 0	11/11	0/11	54 ± 2
Amantadine	3.2	1 ± 1	5/5	0/5	57 ± 2
	10	29 ± 18	7/7	2/7	56 ± 2
	18	37 ± 18	8/8	3/8	53 ± 4
	32	86 ± 14	7/7	6/7	39 ± 8
Lisuride	0.01	33 ± 21	6/6	2/6	61 ± 4
	0.032	47 ± 21	6/6	3/6	56 ± 4
	0.1	54 ± 19	7/7	3/7	44 ± 3
	0.32	84 ± 13	7/7	6/7	27 ± 2
Calcium hopantenate	320	2 ± 1	6/6	0/6	54 ± 2
	560	50 ± 22	6/6	3/6	40 ± 6
	1000	61 ± 24	5/6	3/5	29 ± 12
Dextrorphan	10	50 ± 29	4/4	2/4	60 ± 4
	32	58 ± 24	5/5	3/5	40 ± 12
	56	66 ± 33	3/6	2/3	21 ± 12
Phencyclidine	1.0	20 ± 20	5/5	1/5	60 ± 3
	3.2	25 ± 25	4/5	1/4	45 ± 15

The number of responses made on the NIK-247-appropriate lever was expressed as a percentage of the total session responses. Percent drug-lever responses and response rate are means ± SE. R/N = number of animals that made at least 50 responses/number of animals receiving the drug treatment. D/R = number of animals selecting the drug-lever/number of animals making responses.

TABLE 2

EFFECTS OF AMANTADINE, LISURIDE, DEXTRORPHAN, PHENCYCLIDINE, AND CALCIUM HOPANTENATE ON PERCENTAGE OF DRUG-APPROPRIATE RESPONSES AND RESPONSE RATE IN RATS TRAINED TO DISCRIMINATE 1.8 mg/kg THA FROM SALINE

Compound	mg/kg (IP)	% Responses on drug-lever	R/N	D/R	Responses/min
Saline	–	2 ± 1	12/12	0/12	52 ± 2
Amantadine	10	33 ± 16	9/9	3/9	59 ± 2
	32	62 ± 15	9/9	5/9	34 ± 6
Lisuride	0.01	27 ± 16	7/7	0/7	61 ± 4
	0.032	44 ± 20	7/7	3/7	50 ± 4
	0.1	92 ± 5	7/7	6/7	43 ± 5
Calcium hopantenate	100	39 ± 24	5/5	2/5	59 ± 3
	320	55 ± 19	7/7	4/7	48 ± 3
	560	38 ± 18	8/8	3/8	60 ± 5
	1000	99 ± 1	3/7	3/3	18 ± 9
Dextrorphan	3.2	32 ± 31	3/3	1/3	64 ± 4
	10	56 ± 17	8/8	4/8	52 ± 5
	32	73 ± 16	8/9	6/8	48 ± 9
Phencyclidine	1.0	0 ± 0	5/5	0/5	58 ± 6
	3.2	26 ± 24	4/6	1/4	25 ± 9

The number of responses made on the THA-appropriate lever was expressed as a percentage of the total session responses. Percent drug-lever responses and response rate are means ± SE. R/N = number of animals that made at least 50 responses/number of animals receiving the drug treatment. D/R = number of animals selecting the drug-lever/number of animals making responses.

TABLE 3

EFFECTS OF SCOPOLAMINE, HALOPERIDOL, SCH 23390, AND SULPIRIDE ON THE DISCRIMINATIVE STIMULUS EFFECT OF 10 mg/kg NIK-247

Pretreatment	mg/kg (IP)	% Responses on drug-lever	R/N	D/R	Responses/min
Saline	–	98 ± 1	11/11	11/11	30 ± 5
Scopolamine	0.1	83 ± 17	6/6	5/6	27 ± 4
	0.18	98 ± 1	6/6	6/6	33 ± 7
	0.32	24 ± 19	6/6	1/6	14 ± 4
Haloperidol	0.032	98 ± 1	6/6	6/6	36 ± 6
	0.1	67 ± 18	6/6	4/6	22 ± 8
SCH 23390	0.1	99 ± 0	6/7	6/6	21 ± 7
Sulpiride	100	100 ± 0	3/5	3/3	15 ± 6

The number of responses made on the NIK-247-appropriate lever was expressed as a percentage of the total session responses. Percent drug-lever responses and response rate are means ± SE. R/N = number of animals that made at least 50 responses/number of animals receiving the drug treatment. D/R = number of animals selecting the drug-lever/number of animals making responses.

Table 3 shows the effects of scopolamine and dopamine antagonists on the discriminative stimulus effect of 10 mg/kg NIK-247. Scopolamine at 0.32 mg/kg significantly blocked the NIK-247 stimulus and reduced the response rate. Haloperidol at doses up to 0.1 mg/kg, SCH 23390 at 0.1 mg/kg and sulpiride at 100 mg/kg failed to antagonize the NIK-247 stimulus. Scopolamine also produced a dose-related antagonistic effect on the discriminative stimulus effect of 1.8 mg/kg THA (Table 4). Doses of 0.1 and 0.32 mg/kg scopolamine significantly blocked the THA stimulus and reduced the response rate. None of the dopamine antagonists had a significant effect on the stimulus effect of 1.8 mg/kg THA.

DISCUSSION

Earlier experiments have shown that physostigmine is a potent discriminative stimulus cue in the rat (12,14,15,23,32). However, AChE inhibitors other than physostigmine have not been used as training stimuli in the drug discrimination paradigm. The present study clearly indicates that the centrally active AChE inhibitors NIK-247 and THA serve as stimulus cues. In rats trained to discriminate 10 mg/kg NIK-247 from saline, 3.2 mg/kg of THA substituted for the NIK-247 stimulus. Conversely, substitution for the 1.8 mg/kg THA stimulus required a dose of 10 mg/kg NIK-247. Thus, symmetrical generalization exists between NIK-247 and THA. Both NIK-247 and THA stimuli were substituted for by 0.32–0.56 mg/kg of physostigmine. Shibanoki et al. (28) reported that NIK-247 inhibited AChE activity in the rat brain without affecting ChAT activity, and that the potency of NIK-247 with regard to this effect was about one-third and one-tenth that of THA and physostigmine, respectively. Thus, the relative potency of these three AChE inhibitors with regard to substitution for their discriminative stimuli was almost parallel to their AChE inhibition activity. This result suggests that cholinergic activation resulting from AChE inhibition may underlie the stimulus effects of NIK-247 and THA.

The discriminative stimulus effects of NIK-247 and THA

TABLE 4

EFFECTS OF SCOPOLAMINE, HALOPERIDOL, SCH 23390, AND SULPIRIDE ON THE DISCRIMINATIVE STIMULUS EFFECT OF 1.8 mg/kg THA

Pretreatment	mg/kg (IP)	% Responses on drug-lever	R/N	D/R	Responses/min
Saline	–	99 ± 0	12/12	12/12	42 ± 3
Scopolamine	0.01	82 ± 16	6/6	5/6	55 ± 3
	0.032	67 ± 20	6/6	4/6	39 ± 3
	0.1	18 ± 17	6/6	1/6	32 ± 4
	0.32	1 ± 1	5/5	0/5	13 ± 1
Haloperidol	0.1	91 ± 3	6/6	6/6	21 ± 9
SCH 23390	0.032	99 ± 1	6/6	6/6	34 ± 9
	0.1	92	1/3	1/1	2 ± 1
Sulpiride	100	67 ± 18	7/7	4/7	43 ± 6

The number of responses made on the THA-appropriate lever was expressed as a percentage of the total session responses. Percent drug-lever responses and response rate are means ± SE. R/N = number of animals that made at least 50 responses/number of animals receiving the drug treatment. D/R = number of animals selecting the drug-lever/number of animals making responses.

were significantly blocked by the muscarinic receptor antagonist scopolamine, and were substituted for by the muscarinic agonist arecoline. The stimulus effect of physostigmine has also been shown to be sensitive to blockade by scopolamine and atropine, but not to blockade by the nicotinic antagonist mecamylamine (14,15,32). Likewise, various muscarinic agonists, including arecoline, mimic the physostigmine cue (14,15,32). These findings suggest that the discriminative stimuli elicited by NIK-247 and THA are mediated by muscarinic receptors, as is that of physostigmine.

Calcium hopantenate, which consists of γ-aminobutyric acid (GABA) and pantoyl moieties, substituted for the stimulus effects of NIK-247 and THA. Calcium hopantenate has been reported to bind to GABA receptors, thus enhancing acetylcholine synthesis and release in cholinergic terminals in the cerebral cortex and hippocampus (18,19). This cholinergic-activating action of calcium hopantenate may contribute to its substitution for the stimulus effects of AChE inhibitors.

Muscarinic agonists are known to increase dopamine release in the rat brain (25,27). Both NIK-247 and THA also produce increases in dopamine release and turnover in the rat brain (10,21). Recently, the THA derivative, SM-10888, was reported to increase dopamine release and dopamine metabolite levels that were inhibited by the muscarinic antagonist pirenzepine (20). In this present study, the dopaminergic-activating drugs amantadine (2,6) and lisuride (7,9) also substituted for the NIK-247 and THA stimuli. Thus, the dopaminergic-activating actions of NIK-247 and THA may account for their stimulus cue. However, the NIK-247 and THA stimuli were not blocked by dopamine antagonists, including the D_1 antagonist, SCH 23390, and the D_2 antagonists, haloperidol and sulpiride. These findings, coupled with the complete blockade of the NIK-247 and THA stimuli by scopolamine, suggest that dopaminergic activation resulting from the inhibition of AChE and subsequent activation of muscarinic receptors may be responsible for only part of the discriminative cue induced by NIK-247 and THA.

On the other hand, it has been shown that THA has a binding affinity for the phencyclidine (PCP) site linked to the *N*-methyl-D-aspartate (NMDA) receptor-channel complex (1), and that THA attenuates NMDA neurotoxicity in cortical cell cultures (3). The noncompetitive NMDA antagonist dextrorphan (34) substituted for the discriminative stimulus of THA and its analogue NIK-247. However, PCP by itself failed to substitute for the THA or NIK-247 stimulus. Thus, the mechanisms underlying the substitution of dextrorphan for the THA and NIK-247 cue can not be explained by its action at PCP sites, and remain to be elucidated.

In conclusion, our findings suggest that the discriminative stimulus effects of NIK-247 and THA are mediated by the activation of muscarinic receptors, and that the dopaminergic activity resulting from cholinergic activation may account for some part of both stimuli.

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