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A COMPARISON OF NICOTINE AND STRUCTURALLY RELATED COMPOUNDS AS DISCRIMINATIVE STIMULI

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1 Of seven nicotine-like compounds tested as discriminative stimuli in the rat, only 3-pyridyl-methylpyrollidine (3-PMP) generalized to the stimulus effects of nicotine.

2 3-PMP caused equivalent nicotine-like responding at a dose (800 μg/kg) approximately 4 times that used for the original nicotine discrimination (200 μg/kg). The ED_{50} for 3-PMP was about 5 times that for nicotine.

3 Testing of the compounds as possible antagonists of the nicotine-elicited cue were negative.

4 The nicotine-like cue produced by an 800 μg/kg injection of 3-PMP was effectively blocked by mecamylamine but not by hexamethonium or atropine. Thus, 3-PMP appears to produce generalization to the nicotine cue via action on central nicotinic-cholinoceptors as has been previously reported for the nicotine discriminative stimulus.

5 Mecamylamine blocked the stimulus-effects of 3-PMP (800 μg/kg) and of nicotine (200 μg/kg) with an ED_{50} of 0.32 and 0.20 mg/kg respectively.

Introduction

The ability of nicotine, as well as other psychoactive drugs, to serve as discriminative cues in two-bar operant discrimination tasks has been well documented (Overton, 1971; Schechter & Rosecrans, 1972a; Barry, 1974). The discriminative stimulus procedure consists of training an animal to make a specific behavioural response (i.e., pressing one lever in a two-bar operant box) under the influence of one drug, while making a different response (i.e., pressing the other lever) in the presence of another drug or saline. Discrimination of the nicotine cue is readily learned by rats. Typically, 15 to 20 discrimination training sessions have produced 75% correct drug lever responding (Spencer & Rosecrans, 1977).

The discriminative cue produced by nicotine injection appears to depend upon the central rather than the peripheral effect of the drug since hexamethonium, the peripheral nicotinic (N)-cholinoceptor blocker, did not alter the cueing potency of nicotine (Schechter & Rosecrans, 1971a). Brain area nicotine levels have also been correlated with the strength and duration of the discriminative stimulus (Schechter & Rosecrans, 1971b). In addition, recent findings (Schechter & Rosecrans, 1972b; Rosecrans & Chance, 1977) have suggested that the centrally-produced cue occurs at N-cholinoceptors but not at muscarinic (M)-cholinoceptors. Thus, the discrimination of the nicotinic state is dependent upon relatively specific stimulus effects of the drug.

This research project was undertaken to investigate whether compounds structurally similar to nicotine produce a similar central cue and to elucidate the chemical configuration necessary for the centrally produced nicotine discriminative stimulus. Seven compounds were examined for generalization to the stimulus effects of nicotine. Compounds I to IV, all pyridine derivatives, were tested because they produce nicotine-like responding on avoidance tasks (Barlow, Oliverio, Sato & Thompson, 1970). Compounds V to VII were investigated because of their structural similarity to nicotine and their reported nicotinic effect in the frog rectus muscle preparation (Haglid, 1967). In addition, a procedural guide for comparison of structurally related compounds within a drug discrimination paradigm is outlined.

Methods

Male Sprague–Dawley rats (Flow Labs, Dublin, Virginia) were used in these experiments. All animals were 80 days of age when training was started. These rats were individually housed in wire mesh cages under a 12 h light/dark cycle. Water was available *ad libitum*, while Purina rat chow was rationed to maintain the animals at approximately 80% free feeding weight.

Apparatus

Standard operant test chambers (Lehigh Valley Electronics, Model 1417), fitted with 2 levers at the same end of the chamber, were used for discrimination testing. A dipper for the delivery of liquid reinforcement (0.1 ml) was located between the left and right levers. Sweetened condensed milk, diluted 2:1 with tap water served as the reinforcer. A houselight above the dipper provided dim illumination to the chamber. Each operant test apparatus was housed in a sound insulated chamber (Lehigh Valley Electronics, Model 132-02) and ventilated by an external exhaust fan.

Reinforcement was delivered on a variable interval (VI)-15 s schedule. On the VI-15 s schedule, lever responses are reinforced on a random time interval averaging one reinforcement every 15 s. The total number of responses made on the left and right levers were tabulated on counters. Electromechanical and solid state programming equipment controlled the delivery of reinforcements as well as the accumulation of total responses for the session.

Training procedure

The rats were first trained to discriminate nicotine from 0.9% w/v NaCl solution (saline) (20 training sessions under each state). Initially, the subjects were trained to respond on either lever for a VI-15 s schedule of reinforcement. When responding stabilized, the rats were injected (s.c.) with either 200 μg/kg nicotine (N) or an equal volume (1 ml/kg) of saline (S) in a counterbalanced sequence (NNSS). The administration of saline or nicotine 10 min before testing served as the cue for the reinforced lever. Half of the rats were reinforced on the left bar following saline injections and the right bar following nicotine injections, the remaining rats were reinforced on the opposite bar for each drug condition. No reinforcements were available during the first 2.5 min of each session (15 min). The non-reinforced periods provided data to assess discrimination learning. The subsequent 12.5 min served as daily discrimination training trials and reinforcement was available when responses were made on the drug-correct lever.

Cannulae implantation

Half of the rats were anaesthetized with Nembutal (35 mg/kg; i.p.) and prepared for surgery. Cannulae, constructed from 24 gauge stainless steel hypodermic needles, were stereotaxically implanted in the lateral ventricles (+5.8 A-P, ±1.8 Lat. +2.5 Deep; Pellegrino & Cushman, 1967). Each cannula was obturated with a stylus (31 gauge) and a dust cover constructed from a plastic cap which was threaded to fit the top of the cannula. Following surgery, training was resumed until discrimination stabilized.

Intraventricular (i.c.v.) drug injections were made through a cannula (31 gauge), extending 1 mm beyond the implanted cannulae and connected to a Hamilton microlitre syringe with polyethylene tubing. Drugs were injected into the lateral ventricle at the rate of 1 μl/15 s to a total volume of 5 μl.

Testing procedure

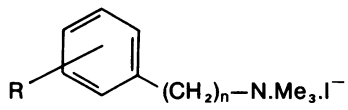
Compounds were tested for generalization and antagonism of the nicotine cue after the response rates and discrimination of the nicotine cue stabilized. Rather than test animals for generalization to the nicotine cue daily, which might risk extinction, generalization sessions were conducted every third day with training sessions continuing on all other days. In order to avoid contamination of the nicotine discrimination, no reinforcements were administered during drug generalization tests. Thus, the rats were injected with the test compound 10 min before being placed in the operant chamber and non-reinforced responding was assessed across the 2.5 min test session.

Drugs

All drug doses administered in this investigation were calculated as the free base and were dissolved in saline to permit equal volume injections (1 ml/kg s.c.; 5 μl i.c.v.). The 98% l-nicotine concentrate was purchased from Aldrich Chemical Corp., mecamylamine hydrochloride was purchased from Merck, Sharp & Dohme, and atropine sulphate and hexamethonium bromide were obtained from the Sigma Chemical Co. Compounds I to IV were donated by Dr R. Barlow, University of Edinburgh, Scotland, and compounds V to VII were donated by Dr H. Erdtman, The Royal Institute of Technology, Stockholm, Sweden.

Generalization studies

To verify the specificity of the stimulus effect of nicotine (200 μg/kg s.c.), generalization to various doses of the drug and also to intraventricular administration was assessed. Generalization was assessed in rats trained to discriminate 200 μg/kg nicotine from saline, 10 min following the administration (s.c.) of 12.5, 25.0, 50.0, 100.0 and 200.0 μg/kg of nicotine. Intraventricular doses of nicotine tested for generalization to the (s.c.) trained cue (200 μg/kg) included: 16, 24 and 32 μg (total volume of injection = 5 μl). Each of these doses was administered in a random order. Comparisons of percentage nicotine-correct responding were made by ED_{50} values calculated for each route of administration.



Compounds tested	R(OH)	n
I	m	3
II	m	1
III	o	3
IV	o	1

Figure 1 Pyridine derivatives tested for nicotine-like activity.

Since the stimulus effect of nicotine could be dependent on any of several structural aspects of the nicotine molecule, compounds of similar structure were also tested for generalization to nicotine. The seven nicotine-like compounds that were tested for generalization to nicotine (200 μg/kg) are shown in Figures 1 and 2. The testing procedure was identical to that previously described for nicotine dose generalization tests. All rats received each of the seven compounds in a random order and all compounds were tested by both the s.c. (200 μg/kg) and the i.c.v. (32 μg) administration routes. Again, the data are expressed as percentage nicotine-correct lever responding.

Dose-generalization curves were obtained for the compound observed to produce the best partial generalization to the stimulus effect of nicotine by both routes of administration, to assess relative potency of that chemical to nicotine. Doses of the compound were tested for generalization by the previously described test procedure. The compound was administered (s.c.) at 50, 100, 200, 400 and 800 μg/kg and (i.c.v.) at 16, 32, 48 and 64 μg. Each rat was tested with all doses by both administration routes in a random sequence. Total responses and percentage nicotine-lever responding were recorded for all test sessions. Maintenance of the original discrimination of nicotine from saline was insured by continuation of training sessions throughout the testing phase.

Antagonism studies

Since drug antagonists are structurally related to their agonists, some of the compounds were examined as possible nicotine antagonists. Testing for nicotine antagonism did not include all of the seven compounds because of the limited quantities available. On the test day a 800 μg/kg s.c. dose of compound II, III, IV or V was administered. Fifteen minutes later, nicotine (200 μg/kg) was injected s.c. Discrimination testing in the operant chamber followed the nicotine injection by 10 min. Each rat was tested under each pretreatment condition once in a random order and percentage nicotine-correct responding was tabulated for each test session.

The stimulus effects of nicotine reportedly can be blocked by pretreatment with mecamylamine, the nicotinic (N)-cholinoceptor blocker but not by the muscarinic (M)-cholinoceptor blocker, atropine, or the peripherally-acting N-cholinoceptor blocker, hexamethonium. Thus, the cue properties produced by nicotine appear specific to the activity of nicotine at central N-cholinoceptor sites. The three blockers, mecamylamine, atropine and hexamethonium were tested as possible antagonists of compound V (3-pyridyl-methylpyrollidine: 3-PMP) to assess the mechanism of generalization to the nicotine cue. Atropine, hexamethonium and mecamylamine were injected subcutaneously in a 1.5 mg/kg dose 10 min before the s.c. injection of 800 μg/kg of compound V. Doses of atropine and hexamethonium were not examined above 1.5 mg/kg since higher doses disrupt response rates and preclude interpretable results with the drug discrimination paradigm. Percentage nicotine responding was assessed in the two-bar discrimination task 10 min after the injection of compound V. Each rat received the three pretreatments in a random order.

The final investigation examined the dose relationships for mecamylamine antagonism of the stimulus effects of both nicotine and compound V. Eight rats received nicotine (200 μg/kg s.c.), while 11 rats were given compound V (800 μg/kg s.c.). Six doses of mecamylamine, 0, 0.125, 0.250, 0.500, 1.00 and 1.50 mg/kg, were given as pretreatment 10 min before the injection of either compound V or nicotine. Each rat was tested in the two-bar discrimination task after receiving each dose of mecamylamine. Percentage nicotine-correct lever responding, total responses and percentage antagonism (% nicotine-lever responding following the agonist only −% nicotine-lever responding following the pretreatment/% nicotine-lever responding following the agonist only −% nicotine-lever responding following saline) of the nicotine cue were tabulated for each treatment combination. Test data from rats not discriminating nicotine from saline during training before test sessions were excluded from the antagonism computation.

Results

Training

After 20 training trials in each drug state, the rats responded 78.6 ± 8.3% on the nicotine-correct lever following nicotine injections and 19.5 ± 7.9% following the injection of saline.

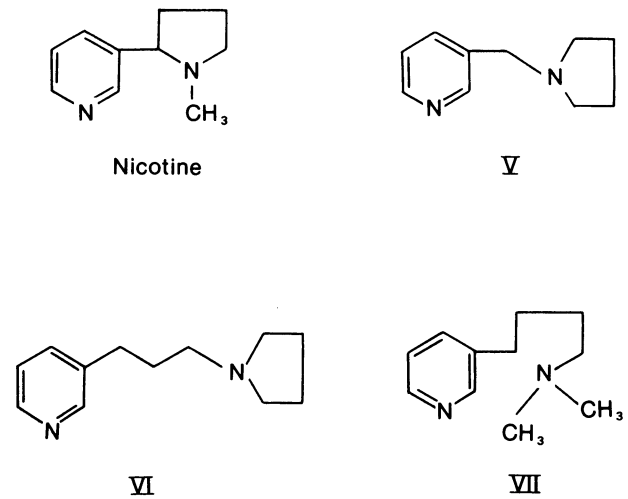


Figure 2 Nicotine derivatives tested for nicotine-like activity.

Generalization studies

Increasing the subcutaneous dose of nicotine produced a graded increase in percentage nicotine-correct responding ranging from 24.8% at 12.5 μg/kg to 78.6% at the training dose of nicotine (200 μg/kg). In addition, partial generalization of the stimulus effects of centrally-administered nicotine to the nicotine discrimination training cue (200 μg/kg s.c.) was observed with 32 μg i.c.v. of nicotine producing 65% nicotine bar responding. Attempts to examine generalization of i.c.v. doses above 32 μg were unsuccessful, since drastic behavioural disruption ensued.

Compounds I to IV did not generalize to the stimulus effect of systemic nicotine (200 μg/kg s.c.) at either 200 μg/kg s.c. or 32 μg i.c.v. doses (Table 1). Although compounds I and III produced no noticeable change in overt behaviour, gross behavioural observations of the rats following the injection of compounds II and IV suggested a facilitation of overt behaviour with the rats being more active and more responsible to external stimuli. Compound II produced partial

Table 1 Generalization of various experimental drugs to nicotine[1,2]

Drug	*Intraventricular % nicotine-correct responding ± s.e.*	*Subcutaneous[3] % nicotine-correct responding ± s.e.*
Nicotine	64.9 ± 6.7	78.6 ± 2.9
Pyridine derivatives:		
I	27.1 ± 13.1	31.6 ± 6.5
II	41.2 ± 6.2	54.4 ± 6.8
III	8.4 ± 4.2	36.1 ± 4.2
IV	18.5 ± 6.1	39.5 ± 6.1
Nicotine derivatives:		
V	45.9 ± 5.1	45.1 ± 7.8
VI	44.4 ± 13.4	18.9 ± 5.1
VII	17.6 ± 4.9	17.6 ± 4.9

[1] The data included in this table are also presented in the *Proceedings from the First International Workshop on the Behavioral Effects of Nicotine*, Zurich, Switzerland (in press). [2] Drugs were administered in doses of 32 μg i.c.v. and 200 μg/kg s.c. Data are presented as mean % responding on the nicotine-correct lever. Drug structures are presented in Figures 1 and 2; n = 12–18. [3] The training dose of nicotine was 200 μg/kg s.c. and all rats were tested on the same VI-15 s schedule of reinforcement.

generalization (categorization suggested by Chance, Murfin, Krynock & Rosecrans, 1977) to the stimulus effects of nicotine following both the s.c. (54% generalization and i.c.v. (41% generalization) routes of administration, but alterations in dose failed to increase percentage nicotine-lever responding. Central injections of compound IV also produced partial generalization to the nicotine cue (42%), but generalization did not follow s.c. injections of compound IV. Of the compounds structurally related to nicotine (compounds V to VII), both compounds V and VI elicited partial generalization (45%) to the nicotine cue when administered intraventricularly, but only compound V was equally effective when administered by either route (Table 1).

Table 2 presents the percentage nicotine-correct lever responding and mean responses per min observed for each dose of compound V tested. Generalization to the nicotine cue decreased as the dose of compound V decreased, indicating the specificity of the nicotine trained cue. Generalization was highest when compound V was administered at 800 μg/kg s.c., producing nicotine-lever responding comparable to the training dose (74% vs 78% responding) of nicotine. Furthermore, response rates were not reduced by this large dose of compound V (800 μg/kg s.c.). Mean percentage nicotine-lever responding was tabulated for each generalization dose tested and ED_{50} values (dose producing 50% nicotine-lever responding) and 95% confidence limits were computed (Litchfield & Wilcoxon, 1949). Calculation of ED_{50} doses for generalization indicate 52.4 μg/kg (95% confidence limits = 23.1 to 118.7) for nicotine and 253.4 μg/kg (95% confidence limits = 122.0 to 568.9) for compound V produced similar results. Thus, a s.c. dose of compound V five times that of nicotine is necessary to produce identical ED_{50} discrimination responding (Figure 3).

Administration of compound V intraventricularly produced minimal generalization to the subcutaneous administration of nicotine. The highest nicotine-correct lever responding occurred following the 32 μg injection of the drug (Table 2). Subsequent increases in dose of compound V failed to enhance the generalization to the nicotine cue but did produce behavioural disruption.

Antagonism studies

As can be seen in Table 3, none of the pretreatments with the nicotine-like compounds significantly blocked the nicotine cue.

Table 3 presents percentage nicotine-correct bar responding observed when compound V was preceded

Table 2 Generalization of compound V (3-PMP) to the nicotine cue[1]

Dose	n	*% nicotine-correct responding ± s.e.*	*Mean responses/ min ± s.e.*
Peripheral nicotine[2]	11	78.6 ± 8.3	9.5 ± 2.3
Peripheral saline	11	19.5 ± 7.9	10.2 ± 3.7
Peripheral administration of compound V (μg/kg):			
50	11	27.5 ± 9.3	14.8 ± 7.2
100	11	27.1 ± 6.9	6.6 ± 1.9
200	11	37.1 ± 8.1	10.6 ± 3.4
400	11	60.5 ± 7.6	13.5 ± 5.7
800	11	73.8 ± 4.9	13.4 ± 4.0
Central nicotine[3]	6	64.9 ± 6.7	11.5 ± 5.7
Central saline	6	25.7 ± 8.9	6.8 ± 1.9
Central administration of compound V (3-PMP) (μg):			
16	6	17.5 ± 7.5	6.3 ± 1.7
32	6	45.9 ± 5.1	7.7 ± 2.2
48	6	35.5 ± 9.9	6.1 ± 2.3
64	6	38.0 ± 18.5	1.6 ± 0.5

[1] All rats were trained to respond on one lever following nicotine injections (200 μg/kg) and on the other lever following saline injections. Reinforcement was delivered on a VI-15 s schedule. [2] Peripheral nicotine was administered in a 200 μg/kg dose. [3] Central nicotine was administered in a total dose of 32 μg.

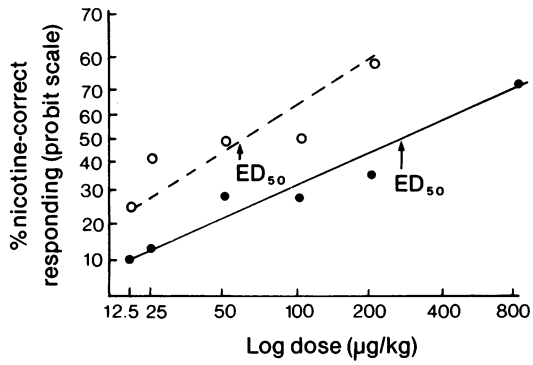


Figure 3 Regression lines for percentage nicotine-correct lever responding for each dose of nicotine (○) and compound V (●) tested for generalization. ED_{50} for nicotine = 52.38 μg/kg; ED_{50} for compound V = 263.40 μg/kg (3-pyridyl-methylpyrollidine).

by each of the cholinoceptor blocking agents. Mecamylamine reduced nicotine-correct bar responding following the administration of compound V to a level of responding, typically observed following saline injection. Thus, the stimulus effects of compound V appear to be mediated by central N-cholinoceptors.

Both percentage nicotine-correct responding and percentage antagonism of the nicotine cue produced by each dose of mecamylamine examined as a blocker of nicotine and compound V are presented in Tables 4 and 5. Mecamylamine continued to block the nicotine cue and the generalization of compound V to the nicotine cue in a dose-dependent manner. The dose of mecamylamine which produced 50% antagonism of the stimulus cue (AD_{50}) was slightly lower for nicotine (AD_{50} = 0.20 mg/kg, 95% confidence limits = 0.14 to 0.29) than for compound V (AD_{50} = 0.32 mg/kg, 95% confidence limits = 0.16 to

Table 3 Possible nicotine and compound V (3-PMP) antagonists[1]

Pretreatment	*Agonist*	n	% *nicotine-correct responding* ± *s.e.*
II (800 μg/kg)	Nicotine	13	74.1 ± 7.6
III (800 μg/kg)	Nicotine	11	67.8 ± 9.0
IV (800 μg/kg)	Nicotine	13	81.4 ± 5.7
V (800 μg/kg)	Nicotine	12	91.9 ± 3.9
Atropine (1.5 mg/kg)	3-PMP	6	65.7 ± 12.5
Hexamethonium (1.5 mg/kg)	3-PMP	6	46.1 ± 10.9
Mecamylamine (1.5 mg/kg)	3-PMP	6	16.5 ± 10.0

[1] All pretreatments were given s.c. and followed 10 min later by the s.c. agonist injection. Testing for % nicotine-correct responding followed the nicotine injection by 10 min.

Table 4 Mecamylamine antagonism of nicotine[1]

Mecamylamine pretreatment	n	% *nicotine-correct responding* ± *s.e.*	% *antagonism of nicotine*
0	8	86.2 ± 6.2	0
0.125 mg/kg	8	75.2 ± 10.8	16.5
0.250 mg/kg	8	41.1 ± 13.7	67.3
0.500 mg/kg	8	20.9 ± 6.8	97.4
1.000 mg/kg	8	21.7 ± 12.3	96.1
1.500 mg/kg	8	9.9 ± 3.2	113.8
Saline[3]	8	19.1 ± 3.2	100.0

[1] All rats were trained to discriminate a 200 μg/kg s.c. nicotine injection from saline injections. [2] Mecamylamine pretreatments were given 10 min before the nicotine injection and testing on the VI-15 s schedule was initiated 10 min after the nicotine injections. [3] Saline data are compiled from animals given s.c. saline only (1 ml/kg).

0.63) when nicotine and compound V doses were approximately equal in cue strength.

Discussion

Compound V (3-PMP) was the only compound examined which generalized completely to the nicotine cue (Tables 1 and 3). Generalization was dependent on the s.c. route of administration and the potency ratio between 3-PMP and nicotine was 5:1. Although rats trained to discriminate s.c. injections of nicotine do generalize to central application of nicotine, central administration of 3-PMP failed to produce significant generalization to the stimulus effects of nicotine. Previous research in our laboratory (Schechter & Rosecrans, 1971b) has indicated that i.c.v. nicotine must be given in a relatively high dose to produce generalization to the stimulus effects of systemic nicotine. We are currently assessing this relative ineffectiveness of the i.c.v. injection by examining the route and rate of absorption of i.c.v. administered nicotine.

Incomplete nicotine generalization resulted from the administration of compound VI and no nicotine generalization was observed with compound VII. Thus, structural manipulations which increase the carbon length between the pyridine and pyrollidine rings (compound VI) or opening the pyrollidine ring (compound VII) both decrease the efficacy of the cue produced by the nicotine molecule. Compound II also elicited partial generalization to the nicotine trained cue. Both compound II and compound V have structural similarities in that the phenyl is separated from the N side chain by one carbon. Thus, increases in the carbon length of the N side chain appear to decrease nicotine-like activity since compounds I, III and VI did not produce nicotine generalization by both administration routes, while generalization to the nicotine cue was dependent on the pyrollidine ring being intact (compound V).

The cue produced by s.c. injections of nicotine is dependent on the integrity of central N-cholinoceptor sites since the nicotine discriminative cue is antagonized by pretreatment with the N-cholinoceptor blocker, mecamylamine (Schechter & Rosecrans, 1971b). Attempts to obviate the cue by blocking M-cholinoceptor sites with atropine have been unsuccessful (Rosecrans & Chance, 1977). Thus, the nicotine discriminative stimulus is relatively specific and dependent on central N-cholinoceptor sites. Comparisons of the antagonism of the nicotine cue and the nicotine-like cue produced by 3-PMP indicate that the cue of both compounds is dependent on their action at central N-cholinoceptor sites (Table 3). Since some difficulty was observed in maintaining the nicotine-saline discrimination during the testing of mecamylamine antagonisms, a better design approach, with respect to testing antagonists, might be to test low doses first rather than exposing the discriminators to a random sequence of pretreatments. Although difficulty was observed when testing mecamylamine antagonism, both the nicotine cue and the nicotine-like cue produced by compound V were blocked by similar doses of mecamylamine (Table 5).

Use of the drug discrimination technique for making comparisons of structurally related compounds is effective as well as specific. The conclusions generated by testing the nicotine-like compounds in the discriminative stimulus paradigm agree with comparisons that have been previously reported for these compounds with other measures. Barlow *et al.* (1970), using the active avoidance paradigm, have observed that compounds II and IV both facilitate active avoidance as does nicotine. Experiments on the nico-

Table 5 Mecamylamine antagonism of compound V (3-PMP)[1]

Mecamylamine pretreatment[2]	n	*% nicotine-correct responding ± s.e.*	*% antagonism of compound V*
0	8	64.9 ± 10.9	0
0.125 mg/kg	9	62.3 ± 5.6	5.9
0.250 mg/kg	8	54.0 ± 10.3	24.8
0.500 mg/kg	7	28.6 ± 11.7	82.7
1.000 mg/kg	9	23.1 ± 7.2	95.2
1.500 mg/kg	7	11.4 ± 6.8	121.9
Saline/Saline[3]	6	21.0 ± 10.7	100.0

[1] All rats were trained to discriminate 200 μg/kg s.c. nicotine injections from saline injections. [2] Mecamylamine pretreatments were given 10 min before compound V injections and testing on the VI-15 s schedule was started 10 min after the compound V injection. [3] Rats were given a saline pretreatment followed 10 min later by a saline injection (1 ml/kg).

tinic effect of these compounds on frog rectus muscle (Haglid, 1967) suggest that compound V is most potent, followed by compound II and compound IV. A similar relationship was observed with our discriminative stimulus paradigm (Table 1).

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