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Pharmacological Studies on *N*-Demethylated Carbachol

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Abstract □ In attempts to find a drug more active than pilocarpine, the tertiary nitrogen derivative of carbachol, *N*-demethylated carbachol, was synthesized and tested on several autonomic nervous system preparations. *N*-Demethylated carbachol was active at muscarinic and nicotinic sites *in vivo* and *in vitro*. In superfusion studies, *N*-demethylated carbachol contracted the smooth muscle of the guinea pig ileum as well as skeletal muscles of frog rectus abdominis and chick biventer cervicis. *N*-Demethylated carbachol decreased blood pressure in the rat, with an ED_{50} (±*SEM*) of 4.82 ± 0.78 mg/kg. After close arterial injection to the cat superior cervical ganglion, *N*-demethylated carbachol elicited contractions of the nictitating membrane (ED_{50} of 1.68 ± 0.24 mg/kg) that were not significantly affected by atropine. *N*-Demethylated carbachol stimulated salivation in dog Wharton duct preparations with an ED_{50} of 2.55 ± 0.81 mg/kg. In contrast, pilocarpine had no effects on skeletal muscles *in vitro*, produced ganglionic effects blocked by atropine, had a prominent effect on salivation, and tended to elevate blood pressure.

Keyphrases □ *N*-Demethylated carbachol—synthesized, cholinergic activity evaluated *in vivo* and *in vitro* □ Carbachol, *N*-demethylated—synthesized, cholinergic activity evaluated *in vivo* and *in vitro* □ Cholinergic activity—*N*-demethylated carbachol evaluated *in vivo* and *in vitro*

It is desirable at times to produce effects that mimic the stimulation of autonomic pathways. One of the simplest ways of achieving this condition, at least in theory, would be administration of the appropriate neurotransmitter to the target organ. Acetylcholine, the transmitter at parasympathetic neuroeffector sites, is virtually useless as a therapeutic agent, largely because of its rapid hydrolysis by both acetylcholinesterase and butyrylcholinesterase. Studies on carbachol, the carbamic acid ester of choline, were reported in 1932 (1). Substitution of the carbamyl moiety in place of the acetyl group of acetylcholine increased resistance to hydrolysis by cholinesterases. At the same time, the essential pharmacological properties of acetylcholine were retained in the new ester.

Clinical use of carbachol has been hindered by the inability of the permanently charged molecule to penetrate biological membranes. Its effectiveness, *e.g.*, as an ophthalmic agent, was maintained only with high concentrations and the addition of wetting agents such as benzalkonium chloride to increase corneal penetration (2). Side effects and toxicity resulting from these procedures have reduced carbachol use in ophthalmology.

Drugs containing a tertiary nitrogen rather than a quaternary nitrogen moiety in their structures have the advantage of higher lipid solubility and can thus penetrate membranes. This ability accounts for the extensive topical use of pilocarpine in glaucoma treatment. This naturally occurring cholinomimetic alkaloid bears little structural resemblance to acetylcholine, however, and certain aspects of its action, mechanism, and inactivation are ambiguous (3).

Considerations of stability, penetrability, and structure suggest that a tertiary nitrogen derivative of carbachol might be an alternative to pilocarpine in ocular therapy.

At least two groups in the past have reported the synthesis of this tertiary nitrogen compound, 2-(dimethylamino)ethyl carbamate (*N*-demethylated carbachol) (I) (4, 5). Despite the therapeutic potential of such a derivative, little work has been done on its pharmacology. Therefore, studies were initiated to investigate its properties.

EXPERIMENTAL

Drugs—Compound I hydrochloride was prepared using a procedure described by Hazard *et al.* (5). Its identity was confirmed by melting point, elemental analysis, and mass and NMR spectral analysis. Acetylcholine iodide[1], atropine sulfate[1], pilocarpine nitrate[1], tubocurarine chloride[1], and carbachol[2] were used as received.

Superfused Guinea Pig Ileum Preparation—Guinea pigs, 300–500 g, were stunned; the terminal portion of the ileum was removed, cleaned, cut into 2-cm long segments, and suspended on a superfusion assembly with an isometric force transducer[3] under an initial tension of 1 g. Tyrode solution (137 m*M* NaCl, 2.7 m*M* KCl, 1.35 m*M* $CaCl_2$, 1.0 m*M* $MgCl_2$, 11.9 m*M* $NaHCO_3$, 0.36 m*M* NaH_2PO_4, and 11.1 m*M* dextrose), oxygenated with 95% O_2–5% CO_2, was pumped over the preparation at a rate of 3–4 ml/min with a peristaltic pump[4]. The superfusion fluid was maintained at room temperature since the ileum displayed less spontaneous activity at 25 than at 37°.

Drugs to be tested were dissolved in saline (0.9% NaCl) and injected directly into the stream of superfusion fluid. Doses were increased in a logarithmic fashion while drug concentrations were adjusted to keep the volume of each dose less than 0.1 ml. The tension developed by the muscle during contraction was recorded on a polygraph[5]. The maximum response of each muscle was taken as 100%, and all smaller responses were ex-

[1] Nutritional Biochemicals Corp., Cleveland, Ohio.
[2] City Chemical Corp., New York, N.Y.
[3] Myograph B, Narco Bio-Systems, Houston, TX 77017.
[4] Polystaltic pump, Buchler Instruments Co., Fort Lee, NJ 07024.
[5] Physiograph model Four-A, Narco Bio-Systems, Houston, TX 77017.

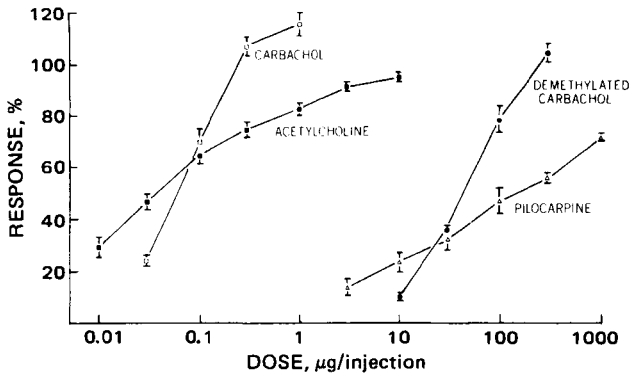

Figure 1—*Dose–response curves of acetylcholine, carbachol, N-demethylated carbachol, and pilocarpine in producing contracture of the smooth muscle of the guinea pig ileum using the superfusion technique. Each point is the mean of five values, and bars represent standard errors.*

pressed as percentages of this maximum response. Dose–response curves were constructed in this manner for acetylcholine, carbachol, pilocarpine, and *N*-demethylated carbachol. In a second set of experiments, dose–response curves for *N*-demethylated carbachol were constructed without and with atropine (1×10^{-8} *M*) in the superfusion fluid.

Superfused Frog Rectus Abdominis Muscle—*Rana pipiens*, 20–25 g, were stunned by a blow to the head, decapitated, and pithed. The rectus abdominis muscle was isolated and mounted for superfusion as described. Frog Ringer solution (110 m*M* NaCl, 2.01 m*M* KCl, 0.77 m*M* $CaCl_2$, 4.25 m*M* $NaHCO_3$, and 11.1 m*M* dextrose), oxygenated with 95% O_2–5% CO_2 at 25°, was used as the superfusion fluid.

Dose–response curves for acetylcholine, carbachol, *N*-demethylated carbachol, and pilocarpine were constructed before and during the treatment with tubocurarine (1×10^{-6} *M*).

Superfused Chick Biventer Cervicis Muscle—Baby chicks, 5–7 days old, were sacrificed with chloroform, and biventer cervicis muscles were dissected away from the body and mounted on superfusion assemblies under 1 g of initial tension. Tyrode solution, oxygenated with 95% O_2–5% CO_2 at 37°, was used for the superfusion fluid.

Experimental details for the construction of dose–response curves were the same as for the superfused guinea pig ileum preparation.

LD_{50} Study in Mice—ICR Charles River mice, 20–30 g, were given *N*-demethylated carbachol intraperitoneally with a microsyringe. The LD_{50} value was calculated according to the method of Litchfield and Wilcoxon (6).

Rat Blood Pressure—Holtzman rats, 300–400 g, were anesthetized with 1.6 g of urethan/kg. The carotid artery was cannulated with a polyethylene tubing attached to a pressure transducer. Drugs were injected through a cannula into the jugular vein, and any resulting changes in blood pressure were recorded on a polygraph[6]. Depressor responses were expressed as the percent change in the mean arterial pressure. Pressor effects were tabulated and analyzed as described later.

Dose–response data for each drug were plotted on log probit paper, and

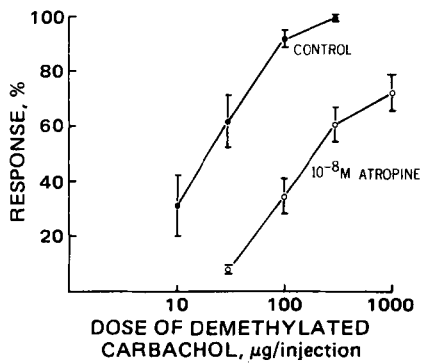

Figure 2—*Effects of atropine on the dose–response curves of N-demethylated carbachol in the superfused guinea pig ileum preparation. Each point is the mean of six values, and bars represent standard errors.*

[6] Model P-1000 A, Narco Bio-Systems, Houston, TX 77017.

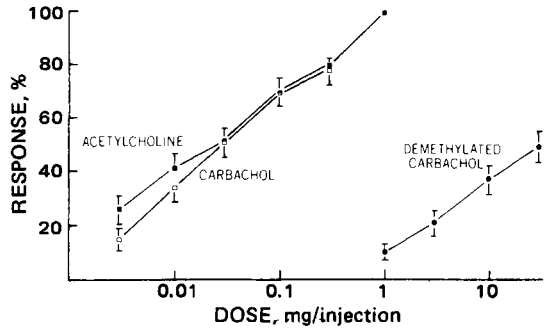

Figure 3—*Dose–response curves of acetylcholine, carbachol, and N-demethylated carbachol in producing transient contracture of the frog rectus abdominis muscle using the superfusion technique. Each point is the mean of six values, and bars represent standard errors.*

regression lines were fitted through the points. The ED_{50} value in each animal was calculated from the parameters of the lines, and values for all animals were then averaged to obtain a mean ED_{50} in this preparation.

Cat Superior Cervical Ganglion Nictitating Membrane—Cats of either sex, 2–3 kg, were anesthetized with 35 mg of pentobarbital sodium/kg intrahepatically. The femoral artery and vein were cannulated for monitoring blood pressure and drug injection. A pair of platinum electrodes was placed around the preganglionic sympathetic nerve fiber. A silk suture was sewn to the nictitating membrane and attached to an isometric force transducer under an initial tension of 1 g. After the lingual and external carotid arteries were tied and divided, a cannula was inserted into the common carotid artery; the ganglion was then perfused at a rate of 0.3–0.4 ml/min with an oxygenated Ringer solution (154 m*M* NaCl, 5.63 m*M* KCl, 1.63 m*M* $CaCl_2$, 5.95 m*M* $NaHCO_3$, and 5.55 m*M* dextrose). Acetylcholine, *N*-demethylated carbachol, and pilocarpine were injected into the same cannula, which was used to perfuse the ganglion.

Injections were given slowly over 1 min and in volumes not exceeding 0.4 ml. The increase in tension of the nictitating membrane following ganglionic stimulation by these agents was recorded on a polygraph. Responses to drugs were expressed as a percentage of the tension developed when the preganglionic trunk was stimulated electrically with monophasic square wave pulses of 10 v, 6 msec, and 20 Hz. Electrical stimulation was also used to test the viability of the preparation throughout the experiment. The methods for handling dose–response data and those of calculating ED_{50} values were identical to those described for rat blood pressure.

Dog Chorda Tympani–Wharton Duct—Mongrel dogs, 13–17 kg, were anesthetized with 40 mg of pentobarbital sodium/kg iv. The femoral artery and vein were cannulated for blood pressure measurements and drug injections. The Wharton duct was cannulated with polyethylene tubing (No. 90), which led to a 100-ml reservoir containing physiological saline. The outflow of the reservoir was positioned over a drop counter for recording on a polygraph.

Platinum electrodes were placed on the chorda tympani nerve, which was stimulated supramaximally for 1 sec every 10 sec with monophasic square wave pulses of 15 v, 2 msec, and 20 Hz. This stimulation produced a mean salivary flow rate of 20 drops/min. The dose producing the

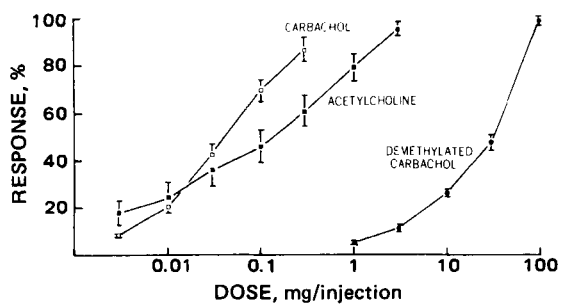

Figure 4—*Dose–response curves of acetylcholine, carbachol, and N-demethylated carbachol in producing transient contracture of the chick biventer cervicis muscle. Each point is the mean of five values, and bars represent standard errors.*

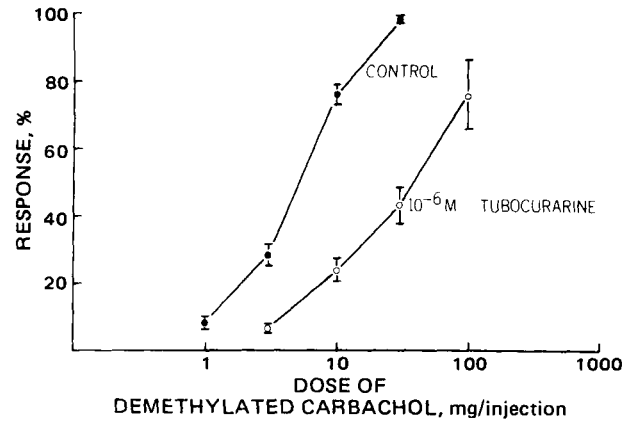

Figure 5—*Effect of tubocurarine on the dose–response curves of* N-*demethylated carbachol in the superfused chick biventer cervicis preparation. Each point is the mean of six values, and bars represent standard errors.*

greatest increase in salivary flow was taken as 100%, and all smaller responses were expressed as percentages of this maximum.

Isotonic saline was infused at a rate of 2 ml/min during the experiment to replace fluid lost through salivation.

Statistical Methods—The significance of differences between two values was tested with the Student *t* test (7).

The significance of differences in *N*-demethylated carbachol and pilocarpine effects on blood pressure in the rat preparation was tested with the following procedure. A 2 × 2 contingency table was constructed for each dose level at which *N*-demethylated carbachol and pilocarpine effects were compared. The number of times each drug dose was administered was recorded; the outcome was classed as a response if an increase in systolic pressure was observed and as a nonresponse if only a depressor effect was noted. The χ^2 procedure of Mantel and Haenzel was used to test the significance of differences between *N*-demethylated carbachol and pilocarpine actions over the entire dose range (8).

RESULTS

***In Vitro* Studies**—*N*-Demethylated carbachol contracted the superfused guinea pig ileum in doses ranging from 10 to 300 μg/injection (Fig. 1). Acetylcholine and carbachol were about 1000-fold more potent than this agent in causing contraction, presumably because of a greater affinity of the cholinergic receptor for quaternary nitrogen-containing compounds (9, 10). The dose–response curves of *N*-demethylated carbachol and carbachol had slopes that were parallel and much steeper than those of acetylcholine and pilocarpine curves. This result suggests that the mechanism of *N*-demethylated carbachol may be similar to that of carbachol but different from that of pilocarpine. This difference in slope of the dose–response curves also necessitates specification of the response level when one compares the potency of *N*-demethylated carbachol and pilocarpine. As can be seen from Fig. 1, *N*-demethylated carbachol is less potent than pilocarpine at low doses but becomes more potent at doses of 100 μg/injection and greater.

Atropine was added to the superfusion fluid to test whether the actions of *N*-demethylated carbachol were produced *via* stimulation of the muscarinic receptor. The dose–response curve obtained with low concentrations of *N*-demethylated carbachol was shifted to the right in a parallel fashion by 10^{-8} *M* atropine (Fig. 2). Higher doses of *N*-demethylated carbachol, however, did not completely reverse the blockade by atropine. Thus, *N*-demethylated carbachol and atropine do not appear to be strictly competitive at the muscarinic site.

Table I—ED_{50} Values of *N*-Demethylated Carbachol and Pilocarpine on *In Vivo* Preparations

Preparation	*N*-Demethylated Carbachol		Pilocarpine	
	n	mg/kg ± *SEM*	*n*	mg/kg ± *SEM*
Cat nictitating membrane	8	1.68 ± 0.84	9	3.10 ± 1.20
Dog Wharton duct	4	2.55 ± 0.81[a]	5	0.08 ± 0.02
Rat depressor response	7	4.82 ± 0.78[a]	7	38.07 ± 4.36

[a] Significantly different from pilocarpine at $p < 0.01$.

Figures 3 and 4 show the effects of *N*-demethylated carbachol on skeletal muscle preparations (frog rectus abdominis and chick biventer cervicis, respectively). The dose–response curves of *N*-demethylated carbachol in both preparations were nearly identical, with 50% maximum contraction evoked by 30 mg/injection. *N*-Demethylated carbachol was about 1000-fold less potent than acetylcholine and carbachol but was more potent than pilocarpine because no stimulation of the somatic fibers was seen with doses of pilocarpine as great as 10 mg/injection. The low solubility of this drug in concentrations greater than 10 mg/100 μl prevented the assay of higher doses. The dose–response curves of *N*-demethylated carbachol and carbachol were parallel, indicating similar mechanisms of action.

Figure 5 illustrates the competitive antagonism of *N*-demethylated carbachol effects at the neuromuscular junction (chick biventer cervicis nerve–muscle preparation) by the nondepolarizing blocker tubocurarine in a concentration of 10^{-6} *M*.

***In Vivo* Studies**—Injection of *N*-demethylated carbachol into the fluid perfusing the superior cervical ganglion resulted in dose-dependent contractions of the nictitating membrane that were immediate in onset and of short duration (Fig. 6). The ED_{50} value for *N*-demethylated carbachol in this preparation was 1.68 ± 0.84 mg/kg and did not differ significantly from the value calculated for pilocarpine (Table I). However, the responses to *N*-demethylated carbachol and pilocarpine differed in a qualitative sense; pilocarpine-induced contractions were delayed in onset, slow to reach a maximum, and of a relatively long duration (Fig. 6).

To determine whether the qualitative differences in *N*-demethylated carbachol and pilocarpine effects might be due to different sites of action in the ganglion, the drugs were readministered after an injection of 1 mg of atropine/kg iv, which is known to block muscarinic, but not nicotinic, receptors. Atropine had a slight effect on responses to 1 or 3 mg of *N*-demethylated carbachol/kg, but the responses to 1 mg of pilocarpine/kg were significantly reduced (Table II). Thus, the main site of pilocarpine action at the ganglion may be at muscarinic receptors whereas that of *N*-demethylated carbachol is not. The responses of the nictitating membrane to *N*-demethylated carbachol were reduced somewhat after atropine, but so were responses elicited by preganglionic electrical stimulation. These results indicate that only a small portion of the effects of *N*-demethylated carbachol as well as presynaptically released acetylcholine is mediated through atropine-sensitive sites that facilitate ganglionic transmission (11).

Figure 7 illustrates the ability of *N*-demethylated carbachol to increase

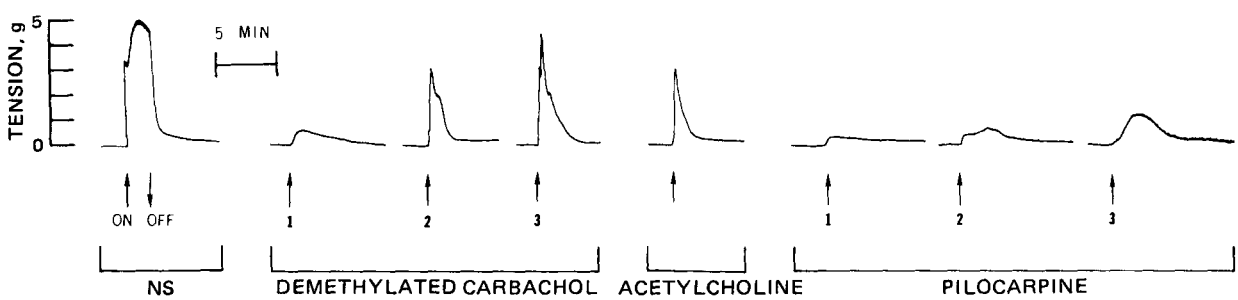

Figure 6—*Contraction of cat nictitating membrane by drugs. Electrical stimulation was applied to the preganglionic sympathic fibers (NS) with parameters mentioned under* Experimental. N-*Demethylated carbachol was administered at 0.1 (1), 0.3 (2), and 1.0 (3) mg/kg; pilocarpine was administered at 0.1 (1), 0.3 (2), and 1.0 (3) mg/kg.*

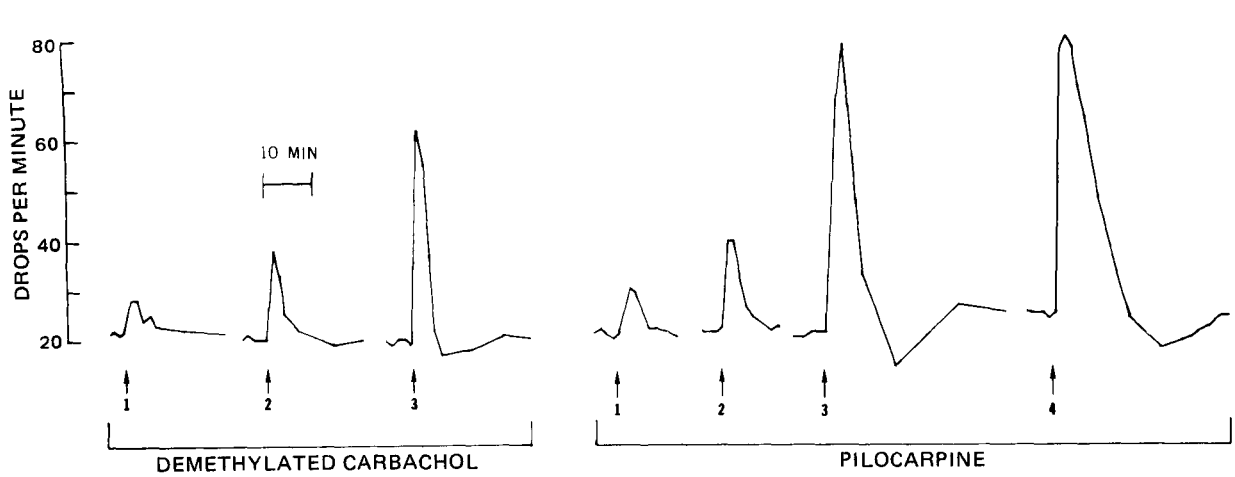

Figure 7—*Effect of drugs on the salivation rate in dog chorda tympani–Wharton duct preparations.* N-*Demethylated carbachol was administered at 0.3 (1), 1.0 (2), and 3.0 (3) mg/kg; pilocarpine was administered at 0.01 (1), 0.03 (2), 0.1 (3), and 0.3 (4) mg/kg.*

the salivation rate in the dog. The compound produced marked decreases in blood pressure in the same range of doses in which it increased salivation (Table I). It was not possible, therefore, to assay doses of *N*-demethylated carbachol that would produce the maximum salivary flow rate without risking the death of the animal. Pilocarpine, however, increased salivation at doses much lower than would have been predicted on the basis of its effects on blood pressure (Table I). The ED_{50} value of pilocarpine was statistically different from that of *N*-demethylated carbachol in the Wharton duct preparation. These results are in accord with the characteristic prominent action reported for pilocarpine on lacrimal, salivary, and sweat glands.

N-Demethylated carbachol was about 10 times more potent than pilocarpine in lowering the mean arterial blood pressure in the rat (Table I). In general, pilocarpine increased the pulse pressure to a greater extent than did *N*-demethylated carbachol. Furthermore, pressor effects were often observed either alone or following the depressor component. These pressor effects were observed following 80% (20 out of 25) of the pilocarpine administrations but were seen in only seven of the 28 instances in which *N*-demethylated carbachol was given. Statistical analysis of these results following the method of Mantel and Haenzel yielded a χ^2 value of 12.31, lending strong support to the notion that the two compounds have different modes of action (8).

The LD_{50} value of *N*-demethylated carbachol in mice was 501 mg/kg with a 95% confidence interval of 434–576 mg/kg. This result may be compared with the LD_{50} value of 500 mg/kg reported for pilocarpine given intraperitoneally to mice (12).

DISCUSSION

The most noticeable consequence of the *n*-demethylation of carbachol is the reduction of drug potency. With the dimethylamino derivative of acetylcholine, 40–300-fold greater concentrations of the tertiary nitrogen compound were required to achieve effects equal to acetylcholine (9, 10). The most encouraging finding of the present study, however, is that the potency of *N*-demethylated carbachol was higher than that of pilocarpine in all preparations tested except the Wharton duct salivation test in which pilocarpine was more potent than *N*-demethylated carbachol.

Table II—Effects of Atropine on Nictitating Membrane Responses

	Control		After 1 mg/kg Atropine	
Treatment	*n*	% Response	*n*	% Response
Electrical stimulation	6	100	6	62 ± 5
N-Demethylated carbachol, 1 mg/kg	6	30 ± 16	5	21 ± 13
N-Demethylated carbachol, 3 mg/kg	6	31 ± 15	6	26 ± 15
Pilocarpine, 1 mg/kg	6	27 ± 5	6	4 ± 2[a]

[a] Significantly different from control at $p < 0.01$, two-tailed test. Drug responses are expressed as percent of preatropine electrical stimulation response ± *SEM*. The absolute reading of the control electrical stimulation response was 45.9 ± 2.4 mm.

The antagonism of *N*-demethylated carbachol effects in the skeletal and smooth muscle preparations by low concentrations of tubocurarine and atropine indicates that the action mechanism of *N*-demethylated carbachol involves the cholinergic receptor. It does not reveal, however, whether the muscle stimulation is produced entirely by direct combination of drug with receptor or whether indirect mechanisms, such as the release of acetylcholine from the presynaptic nerve terminal or cholinesterase inhibition, are also involved. Further studies are planned to elucidate the action mechanism of *N*-demethylated carbachol.

Results from *in vitro* experiments indicate that *N*-demethylated carbachol, like carbachol and acetylcholine, stimulates both muscarinic and nicotinic sites. A characteristic feature of nicotinic receptors is that they generally require higher quantities of drug for stimulation than muscarinic receptors. This quality is illustrated in superfusion studies where doses of agonist 1000 times higher than those acting on guinea pig ilea were necessary to achieve contraction of the rectus abdominis and biventer cervicis muscles. Pilocarpine, on the other hand, seems to be devoid of any nicotinic activity.

In *in vivo* studies, *N*-demethylated carbachol again exerted both muscarinic and nicotinic actions. Doses of atropine that completely abolished the salivation and depressor effects of *N*-demethylated carbachol had little effect on the *N*-demethylated carbachol response on the nictitating membrane preparation, indicating that *N*-demethylated carbachol was acting at nicotinic receptors in the superior cervical ganglion. The ED_{50} of *N*-demethylated carbachol in this preparation, however, was not significantly different from the value in Wharton duct or blood pressure preparations in which *N*-demethylated carbachol effects were mediated through muscarinic receptors. The lower sensitivity expected for nicotinic sites in the sympathetic ganglion may have been offset by higher local concentrations of agonist resulting from close arterial drug injection.

In these studies, atropine blocked the effects of pilocarpine at the ganglion, as has been shown in the past (13, 14). Trendelenburg (15) demonstrated that pilocarpine's actions were unaffected by hexamethonium in doses that abolished membrane responses to preganglionic stimulation and intraarterial acetylcholine. Pilocarpine thus appears to be acting at ganglionic muscarinic receptors to produce nictitating membrane contraction.

While both *N*-demethylated carbachol and pilocarpine produced dose-dependent decreases in arterial pressure, over half of the intravenous injections of pilocarpine were followed by a secondary rise in blood pressure. This pressor response was abolished by atropine and α-adrenergic antagonists (16), ganglion depolarizing agents (17, 18), catecholamine depletion, and prevention of norepinephrine release from sympathetic terminals (18) but was unaffected by adrenalectomy (16, 17). Therefore, this secondary rise in pressure may result from stimulation of muscarinic receptors in sympathetic ganglia. Sympathetic activation may be responsible, at least in part, for the higher ED_{50} value of pilocarpine compared with that of *N*-demethylated carbachol in the rat blood pressure preparation, since this action would produce effects on the heart and blood vessels in opposition to those of direct vascular muscarinic depressor action.

The dog Wharton duct salivation preparation was the only instance in which pilocarpine was more potent than *N*-demethylated carbachol.

However, this prominent action of pilocarpine on salivary and other exocrine glands constitutes an undesirable effect in most cases (19). Stimulation of lacrimal glands following instillation of pilocarpine into the conjunctival sac would conceivably enhance its removal by tears into the nasolacrimal duct, thereby reducing its ocular penetration and increasing systemic absorption. These effects should be less evident with *N*-demethylated carbachol.

The use of the LD_{50}/ED_{50} ratio to compare the margin of safety of two drugs is not valid in instances where the slopes of the dose–response curves for toxicity and/or effect of the drugs are not parallel. For this reason, the observation of equal LD_{50} values for pilocarpine and *N*-demethylated carbachol does not necessarily imply that they have equal margins of safety. In addition, determinations of lethality may give no indication of the tendency of a drug to produce side effects. In this regard, preliminary studies showed marked irritation of the canine eye following topical application of a 1% pilocarpine solution while no irritation was observed after similar applications of *N*-demethylated carbachol in concentrations as high as 4%[7].

In summary, the tertiary nitrogen-containing analog of carbachol was tested and found to be an effective cholinergic stimulant active at both muscarinic and nicotinic sites. Unlike pilocarpine, *N*-demethylated carbachol shows less tendency to produce exocrine gland and sympathetic effects, properties that should make it a useful alternative to pilocarpine. Both compounds are currently being evaluated in a canine model of glaucoma.

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Effects of Compression Force, Particle Size, and Lubricants on Dissolution Rate

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Abstract □ The effects of compression force, particle size, and lubricant concentration on the dissolution rates of compressed disks of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid were investigated. Compression forces from 450 to 9100 kg had no effect on dissolution rates. With 5% starch incorporated into an equimolar mixture of aspirin and salicylic acid, the dissolution rates were independent of compression forces from 910 to 9100 kg. A 10-fold change of particle size of the materials being compressed did not affect the dissolution rates. An increase in the concentration from 0.1 to 5% of calcium stearate, glyceryl monostearate, magnesium stearate, and stearic acid progressively slowed the dissolution rate. An increase in the concentration from 0.1 to 5% talc and polyethylene glycol 4000 did not affect the dissolution rates. An increase in the concentration of starch from 0.1 to 5% progressively increased the dissolution rates.

Keyphrases □ Dissolution rate—compressed disks of salicylic acid, aspirin, and equimolar mixture, effects of compression force, particle size, and lubricants □ Compression force—effect on dissolution rate of compressed disks of salicylic acid, aspirin, and equimolar mixture □ Particle size—effect on dissolution rate of compressed disks of salicylic acid, aspirin, and equimolar mixture □ Lubricants, various—effect on dissolution rate of compressed disks of salicylic acid, aspirin, and equimolar mixture □ Salicylic acid—compressed disks alone and equimolar mixture with aspirin, dissolution rate, effects of compression force, particle size, and lubricants □ Aspirin—compressed disks alone and equimolar mixture with salicylic acid, dissolution rate, effects of compression force, particle size, and lubricants

The kinetics of dissolution for pure materials and for two-component solids have been published (1–5). Various relationships between dissolution rate and compression force have been reported (6–11). As Knoechel *et al.* (12) suggested, although compression force may influence the dissolution rate, the formulation and the particular medicinal compound have a greater effect.

Finholt and Solvang (13) studied the effect of particle size of granules used to prepare phenacetin tablets on the dissolution rate. The rate was increased in diluted gastric