# The Stimulation of Canine Prostatic Secretion by Substances With Ganglion-Stimulating Actions* (33631)

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The ability of drugs to stimulate secretion of the prostate gland of the dog has not received much study. In 1937, Farrell and Lyman (1) reported that nicotine, pilocarpine, acetylcholine, and epinephrine provoked secretion, while more recently it was observed that secretion can be provoked by a number of parasympathomimetic substances (2), but that the ability of sympathomimetic amines to stimulate secretion is quite limited (3). The present experiments concerned secretory responses of the canine prostate gland to three substances which are known to possess ganglion-stimulating actions: nicotine, the ganglionic action of which is blocked by hexamethonium but not by atropine or cocaine, and 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (Mc N-A-343) and *N*-benzyl-3-pyrrolidyl acetate methobromide (AHR-602), which stimulate ganglia by an action not blocked by hexamethonium but blocked by both atropine and cocaine (4–7). A summary of some of these experiments was already published (8).

*Methods.* These experiments were performed on nine unanesthetized mongrel dogs which weighed between 10.0 and 20.9 kg. Prostatic fluid was collected *via* fistulas produced by cystopreputiostomy—removal of the penis from the sheath at its proximal attachment, separation of the bladder and prostate gland and attachment of the preputial sheath to the bladder (9). In these animals the nerve and blood supplies to the gland remained intact. All dogs were castrated and maintained on 5 mg of testosterone daily. Experimentation was begun only after complete recovery from the surgical procedures. During each experiment the dog was restrained on a table in a standing position and the prostatic fluid was collected into a graduated tube in four 15-min serial samples starting at the time of injection of the drug under study. Heart rate was monitored at the same time by asucultation. There was at least a 2-day interval between successive experiments on the same animal and only one dose of ganglion-stimulating drug and one dose of blocking agent were administered on any 1 day. All of these dogs were necropsied at the end of these experiments, and the prostate glands of these dogs weighed between 17.1 and 77.0 g.

The drugs used were pilocarpine hydrochloride, nicotine (base), 4-(m-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343), *N*-benzyl-3-pyrrodilyl acetate methobromide (AHR-602), atropine sulfate, hexamethonium chloride dihydrate and cocaine hydrochloride. All doses refer to the salt except those of nicotine which refer to the base.

*Results. Spontaneous and pilocarpine-induced prostatic secretion.* The prostate gland of the dog under resting conditions has been previously found to secrete fluid at a slow, constant rate of 0.1–2.0 ml/hr (10). In the animals used in these experiments there was also a slow spontaneous secretion by the prostate gland. Volumes of 0.5–1.4 ml were collected during 1-hr collections following the intravenous administrations of saline (Table I).

Since pilocarpine has been repeatedly observed to stimulate prostatic secretion (1, 10, 11), the secretory responses of all of the dogs to the intravenous administration of 0.7 mg/kg of pilocarpine was determined for comparison with responses to other drugs. This dose of pilocarpine produced a pro-

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TABLE I. The Secretion of Canine Prostatic Fluid in Response to Pilocarpine and Ganglion-Stimulating Substances.[a]

| Drug | Dose (mg/kg) | Rte of adm | No. of dogs | Volumes of secretion (ml) | | | | | Additional effects | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0–15 min | 15–30 min | 30–45 min | 45–60 min | 0–60 min | Salivation | Lacrimation | Tachycardia | Emesis | Other |
| Saline | 0.2[b] | i.v. | 6 | 0.3 ± 0.02 | 0.2 ± 0.02 | 0.2 ± 0.06 | 0.2 ± 0.10 | 0.8 ± 0.14 | None | None | None | None | None |
| Pilocarpine hydrochloride | 0.7 | i.v. | 9 | 21.1 ± 2.5 | 12.1 ± 2.2 | 5.0 ± 0.8 | 3.8 ± 0.4 | 41.9 ± 4.4 | 8/9[c] | 8/9 | 3/9 | 3/9 | None |
| Nicotine | 0.3 | s.c. | 4 | 0.3 ± 0.4 | 0.1 ± 0.02 | 0.1 ± 0.05 | 0.1 ± 0.04 | 0.6 ± 0.12 | None | None | None | None | None |
| | 1.0 | s.c. | 4 | 0.8 ± 0.4 | 0.5 ± 0.2 | 0.6 ± 0.3 | 0.1 ± 0.08 | 2.0 ± 0.8 | None | 4/4 | None | 4/4 | Tachypnea (1/4) |
| | 3.0 | s.c. | 6 | 3.0 ± 1.1 | 0.4 ± 0.10 | 0.4 ± 0.08 | 0.4 ± 0.05 | 4.1 ± 1.1 | 3/6 | 6/6 | 0/6 | 6/6 | Tachypnea (5/6); relaxed nictitating membranes (6/6); transient prostration (2/6); piloerection (1/6); tremor (1/6) |
| McN-A-343 | 0.3 | i.v. | 4 | 5.5 ± 2.0 | 0.4 ± 0.08 | 0.4 ± 0.12 | 0.3 ± 0.08 | 6.6 ± 2.0 | 4/4 | None | None | None | None |
| | 1.0 | i.v. | 5 | 9.1 ± 2.6 | 0.5 ± 0.1 | 0.2 ± 0.04 | 0.3 ± 0.03 | 10.4 ± 2.4 | 4/5 | None | 1/5 | 2/5 | Piloerection (1/5) |
| | 3.0 | i.v. | 4 | 24.2 ± 3.9 | 0.8 ± 0.1 | 0.8 ± 0.2 | 0.8 ± 0.3 | 26.6 ± 4.3 | 3/4 | 3/4 | 3/4 | 3/4 | Tachypnea (3/4); relaxed nictitating membranes (2/4); piloerection (3/4); tremor and transient prostration with marked diarrhea and abdominal sounds (1/4) |
| AHR-602 | 1.0 | i.v. | 3 | 1.1 ± 0.7 | 0.3 ± 0.2 | 0.2 ± 0.1 | 0.1 ± 0.1 | 1.8 ± 0.5 | 3/3 | None | None | None | None |
| | 3.0 | i.v. | 3 | 4.7 ± 0.2 | 0.7 ± 0.4 | 0.7 ± 0.4 | 0.6 ± 0.4 | 6.6 ± 1.1 | 3/3 | None | None | None | None |
| | 10.0 | i.v. | 3 | 15.6 ± 2.2 | 0.5 ± 0.3 | 0.3 ± 0.1 | 0.2 ± 0.03 | 16.8 ± 2.5 | 3/3 | None | None | 1/3 | Piloerection (2/3) |
| | 30.0 | i.v. | 1 | 23 | 2.0 | 2.2 | 0.6 | 27.7 | 1/1 | None | None | None | Piloerection, tremor and transient prostration (1/1) |

[a] Each value represents the mean ± SE or the individual values.

[b] (ml/kg) instead of (mg/kg).

[c] Number refers to number of dogs.

nounced secretion of prostatic fluid accompanied by salivation, tachycardia, lacrimation, and emesis (Table I).

*Responses to nicotine.* A single dose of 0.3 mg/kg of nicotine was given intravenously to one dog and this produced prostration and extreme muscle tremor for approximately 0.5 hr. During the first hour after treatment this dog secreted 3 ml of prostatic fluid. A second dog was then given 0.1 mg/kg intravenously and again this was followed by prostration, although in this instance it lasted for only 3 minutes. This dog secreted 2 ml of prostatic fluid in the first hour following treatment. Thus, it appeared that nicotine could not be given intravenously at doses which would stimulate prostatic secretion without producing other profound effects. Accordingly, in another series of experiments nicotine was given subcutanously at doses of 0.3, 1, and 3 mg/kg (Table I). These doses of nicotine produced a dose-related increase in prostatic secretion. The two highest doses produced emesis in each instance, while the highest dose also produced tachypnea, relaxation of the nictitating membranes, piloerection, tremor, and transient prostration. Although the secretory responses to 3 mg/kg were quite small compared to those of pilocarpine (Table I), it was felt that this was the largest dose of nicotine which could be readily tolerated by these dogs and no attempt was made to study the effect of larger doses.

*Responses to McN-A-343.* The intravenous administration of 0.3–3 mg/kg of McN-A-343 stimulated prostatic secretion and at the same time produced salivation, tachycardia, lacrimation, emesis, piloerection, tremor, tachypnea, and relaxation to the nictitating membranes (Table I). In one dog the highest dose produced these effects and also produced tremor and transient prostration with marked diarrhea and abdominal sounds. In all animals the secretory responses were very pronounced but very brief. They began immediately after injection and were esentially complete within 15 min (Table I).

*Responses to AHR-602.* The intravenous administration of 1–30 mg/kg of AHR-602 produced a dose-related secretion of prostatic fluid accompanied by salivation, lacrimation, emesis, piloerection and, at the highest dose, tremor and prostration (Table I). As with McN-A-343, the secretory responses began almost immediately after injection and were of short duration.

*Effects of blocking agents on the secretory responses to nicotine, McN-A-343, and AHR-602.* Table II summarizes a brief series of experiments in which hexamethonium, atropine, and cocaine were given in attempts to reduce or abolish the secretory response to these ganglion-stimulating substances. While the number of experiments is admittedly small, due primarily to the inability of these unanesthetized animals to tolerate large doses of nicotine and cocaine, treatment with hexamethonium consistently reduced the response to nicotine but did not alter the responses to McN-A-343 or AHR-602; pretreatment with cocaine did not alter the response to nicotine, appeared to potentiate the response to McN-A-343 and did not affect the response to AHR-602; and pretreatment with atropine consistently reduced the responses to all three stimulants.

*Discussion.* Substances can stimulate ganglia by at least two separate actions. The best known of these, referred to as a nicotinic action because it is characteristically produced by nicotine, is blocked by hexamethonium but not by cocaine or low doses of atropine, while the other ganglion-stimulating action has been called nonnicotinic because it is not produced by nicotine and it is not blocked by hexamethonium; it is blocked, however, by cocaine or low doses of atropine (4). In the present study McN-A-343 and AHR-602 were chosen for comparison with nicotine because they have been reported to exert a nonnicotinic stimulating action upon sympathetic adrenergic fibers (5–8).

A basis for anticipating that substances which stimulate ganglia might provoke prostatic secretion lies in the observations that although the electrical stimulation of the pelvic nerves does not provoke secretion, marked secretory response are obtained upon stimulation of the hypogastric nerves (1, 12). Further observations indicate that the involved fibers are cholinergic in nature be-

TABLE II. Effects of Some Blocking Agents on the Stimulation of Canine Prostatic Secretion by Nicotine, McN-A-343 and AHR-602.[a]

| Agonist | | | | Antagonist | | | |
|---|---|---|---|---|---|---|---|
| Drug | Dose (mg/kg) | Route | Dog no. | None (agonist alone) | Hexamethonium hydrochloride dihydrate (10 mg/kg, i.m., at 0 time)[b] | Atropine sulfate (0.1 mg/kg, i.v., at −5 min)[c] | Cocaine hydrochloride (10 mg/kg, s.c., at −30 min)[d] |
| Nicotine | 3.0 | s.c. | 1 | 4.2 | 0.5 | — | — |
| | | | 2 | 8.9 | 1.4 | 4.0 | — |
| | | | 3 | 2.3 | 0.4 | 0.5 | — |
| | | | 4 | 2.3 | 0.5 | 1.6 | — |
| | | | 5 | 1.5 | 0.8 | — | 4.6 |
| | | | 6 | 5.5 | — | — | 5.3 |
| McN-A-343 | 3.0 | i.v. | 2 | 21.7 | 20.5 | 1.6 | 30.7 |
| | | | 3 | 17.6 | 21.6 | 1.3 | 37.3 |
| AHR-602 | 10.0 | i.v. | 1 | 18.2 | 18.0 | 1.4 | 18.0 |
| | | | 4 | 12.0 | 9.5 | 1.2 | 13.3 |

[a] Each value represents the volume of prostatic fluid (ml) secreted in the first 60 min after administration of the agonist, which was given at zero time.

[b] This dose of hexamethonium relaxed the nictitating membranes of all animals.

[c] This dose of atropine produced a marked tachycardia in all animals.

[d] This dose of cocaine produced severe hyperthermic responses in all animals.

cause the response is blocked by atropine, histochemical examinations fail to reveal adrenergic neurons terminating on secretory cells, and because the gland secretes copiously in response to cholinergic drugs but not to sympathomimetic amines (2). Thus, the possibility that nicotine, McN-A-343, and AHR-602 might stimulate these sympathetic cholinergic fibers was examined.

It was found that nicotine produced distinct but very small secretion responses, even following doses of nicotine which produced profound effects upon other structures. Similar responses to similar doses of nicotine were reported by Farrell and Lyman (1). Thus, it appears that the sensitivity of the prostate gland to nicotine is quite limited.

The responses to McN-A-343 and AHR-602, in contrast, were very marked, although very brief, and occurred following doses of these agents which did not produce severe systemic effects,. However, it is not certain that this secretion resulted from a nonnicotinic ganglion-stimulating action, for although the responses appeared to be blocked by low doses of atropine they were not blocked by doses of cocaine which are known to block other effects of these same compounds which result from ganglionic stimulation (5–7). It is more likely that these secretory responses result from a direct cholinomimetic action which these drugs can produce. although these actions generally are not prominent (5, 6).

In addition to these observations, the possibility that secretory fibers innervating the prostate gland of the dog are insensitive to the nonnicotinic ganglion-stimulating action of drugs is further supported by the observations that the marked secretory responses of this gland to pilocarpine are not reduced by morphine or cocaine (11), although both of the substances are know to block the nonnicotinic effects of pilocarpine upon other fibers (4).

*Summary.* The stimulation of prostatic secretion by nicotine, 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343) and *N*-benzyl-3-pyrrolidyl acetate methobromide (AHR-602) was studied in unanesthetized, castrated, testosterone-treated dogs with surgically prepared fistulas

which allowed the collection of prostatic fluid uncontaminated by urine. The subcutaneous administration of 0.3, 1, or 3 mg/kg of nicotine provoked the secretion of only small amounts of prostatic fluid accompanied by tachycardia and emesis; the highest dose also produced tachypnea and relaxation of the nictitating membranes. The intravenous administration of 0.3, 1, or 3 mg/kg of McN-A-343 produced a moderate secretion of prostatic fluid accompanied by salivation, lacrimation, emesis, piloerection, and variable effects on heart rate. The intravenous administration of 1, 3, 10, or 30 mg/kg of AHR-602 produced a moderate prostatic secretion accompanied by salivation and piloerection. Atropine reduced the prostatic secretion in response to all three agents; hexamethonium reduced the secretory response to nicotine only; and cocaine did not reduce the secretory response to any of these drugs.

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