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# Effects of Dopamine on the Gastrointestinal Tract of Chicks

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**Abstract**—The effects of dopamine on the gastrointestinal tract of chicks have been investigated. Dopamine caused concentration-related contractions of the upper oesophagus, crop or lower oesophagus but relaxed the duodenum, ileum, large intestine or caecum in a concentration-related fashion. By means of specific antagonists, the presence of muscarinic, histamine ($H_1$), α-adrenergic, 5-HT-ergic and dopaminergic receptors were established in the lower oesophagus and their stimulation caused contraction while β-adrenergic-receptor stimulation caused relaxation. Contraction of the lower oesophagus induced by dopamine was abolished by lysergic acid diethylamide and was antagonized by moderate concentrations of haloperidol or pimozide. Tachyphylaxis developed to repeated administration of a large concentration of dopamine. These findings suggest that contraction of the lower oesophagus of chicks by dopamine is largely mediated by 5-hydroxytryptamine release and that stimulation of dopaminergic receptors contributes to a lesser extent.

The gastrointestinal tract consists of various segments which are contracted by parasympathetic stimulation while the sympathetic system relaxes most of its segments (Rang & Dale 1991). It could therefore be used to examine the effects of dopamine on peripheral, non-vascular smooth muscle. Another advantage of using the gastrointestinal tract is its segmentation which would allow a systematic, comparative study of the effects of dopamine within one system.

## Materials and Methods

Chicks of either sex, aged from 2–7 days after hatching, were starved overnight then killed by an overdose of ether. After cutting open the thorax and abdomen, the whole gastrointestinal tract was removed without stretching and placed in a beaker containing Krebs solution continuously bubbled with 95% $O_2$–5% $CO_2$. The solution was changed every 30 min.

For any segment of the tract used in this study, 1–2 cm length was cut and cleared of faecal contents and the surrounding connective tissue, with care being taken to avoid stretching the tissue. The tissue was then threaded at both ends, one end was tied to a pin held in a Perspex block and suspended in the organ bath, while the other end was tied to an isotonic transducer, under 2 g tension, connected to a flat-bed pen recorder (Servoscribe).

The organ bath contained 50 mL of freshly prepared physiological saline (composition (mM): NaCl 118·0, KCl 4·7, $MgSO_4$ 2·5, $NaH_2PO_4$ 1·0, $NaHCO_3$ 30·0, glucose 11·1, $CaCl_2$ 2·5) gassed with 95% $O_2$–5% $CO_2$. The bath was maintained at 32 ± 1°C by means of a water jacket connected to a thermostatically-controlled pump (Haake). Tissues were given 30 min to equilibrate before experiments started.

*Preliminary studies*

Using the oesophagus, the temperature of the organ bath was found to influence the rhythm of the gastrointestinal tract, hence the temperature of 32°C (Bowman & Everett 1964) was chosen and subsequently used throughout this study.

It was observed that for various segments of the tract, responses to drugs were better with chicks starved overnight than for unstarved animals. Therefore, chicks were always starved overnight in investigations reported in this study.

Dopamine caused dose-dependent contractions of the lower oesophagus and relaxations of the large intestine of Rhode Island Red chicks, White Leghorn chicks and Broiler chicks, indicating that its effects are qualitatively similar for different strains of chicks. Rhode Island Red chicks, obtained from the National Veterinary Research Institute, Vom, Nigeria, were subsequently used in the present study.

When dose-response curves to dopamine, acetylcholine and noradrenaline were established for the lower oesophagus and large intestine from chicks aged between 2 days and 4 weeks post-hatching, the best responses were observed for chicks aged 2–7 days and this was the age range used in the present study.

*Effects of dopamine, acetylcholine and noradrenaline on segments of the gastrointestinal tract*

Using the above parameters, the effects of increasing concentrations of dopamine, acetylcholine and noradrenaline on various segments of the tract were determined.

The crop was opened by a longitudinal cut in the wall of the attached portion of the oesophagus and a strip of tissue about 3 mm wide cut transversely from the middle of the opened crop (Everett 1964) was used. Responses to drugs were then taken for the normal (unstretched) or stretched (with the tissue kept under 4 g tension) crop (Everett 1964).

Segments of the duodenum were taken 1 cm away from the gizzard while ileal segments were taken about 4 cm away from the ileuo-duodenal junction.

*Mechanism of action of dopamine in the lower oesophagus*

Dose-response curves to various agonists were constructed from which concentrations producing suitable submaximal

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responses were chosen. The minimum concentrations of the specific antagonists required to block the responses to the agonists were also determined from the antagonist concentration-response curves. The dose of dopamine that closely matched the response of the oesophagus to each agonist drug was then determined and challenged with the same concentration of the specific antagonist.

The possibility that the actions of dopamine were mediated by specific dopaminergic receptors was investigated using two centrally acting dopaminergic receptor antagonists, pimozide and haloperidol (Rang & Dale 1991). The initial part of this investigation involved the determination of suitable concentrations and drug contact times for the antagonists. From the concentration-response curves to dopamine in the presence and absence (control) of the antagonists, suitable antagonist concentrations were chosen. Such antagonist concentrations were administered against a dose of acetylcholine that produced a comparable contraction of the oesophagus to the concentration of dopamine used, so as to determine whether the antagonistic actions of pimozide and haloperidol were selective for dopamine.

Since pimozide solution was prepared as a solution in Tween 80, the effect of Tween 80 against dopamine was also determined.

*Drugs*

Drug solutions were freshly prepared in concentrations such that the addition of 0·5 mL gave the required final bath concentration. The drug contact time was 1 min with an interval between successive doses of at least 5 min. Concentration response-curves were established by graded increases in the concentrations of agonist or antagonist drugs. Antagonists were always applied 5 min before the agonists.

Drugs used were acetylcholine bromide (BDH, Poole, UK), atropine sulphate (Sigma, Poole, UK), dopamine hydrochloride (Sigma), haloperidol (G. D. Searle & Co. Ltd, Darmstadt, Germany), histamine acid phosphate (BDH, Poole, UK), isoprenaline hydrochloride (BDH, Poole, UK), lysergic acid diethylamide or LSD (Sandoz, Basel, Switzerland), mepyramine maleate (May & Baker, Dagenham, UK), noradrenaline birtartrate (Sigma), phentolamine mesylate (Ciba-Geigy, Summit, NJ), pimozide (Sigma), propranolol hydrochloride (ICI, Macclesfield, UK), 5-hydroxytryptamine creatinine sulphate (5-HT) (Sigma).

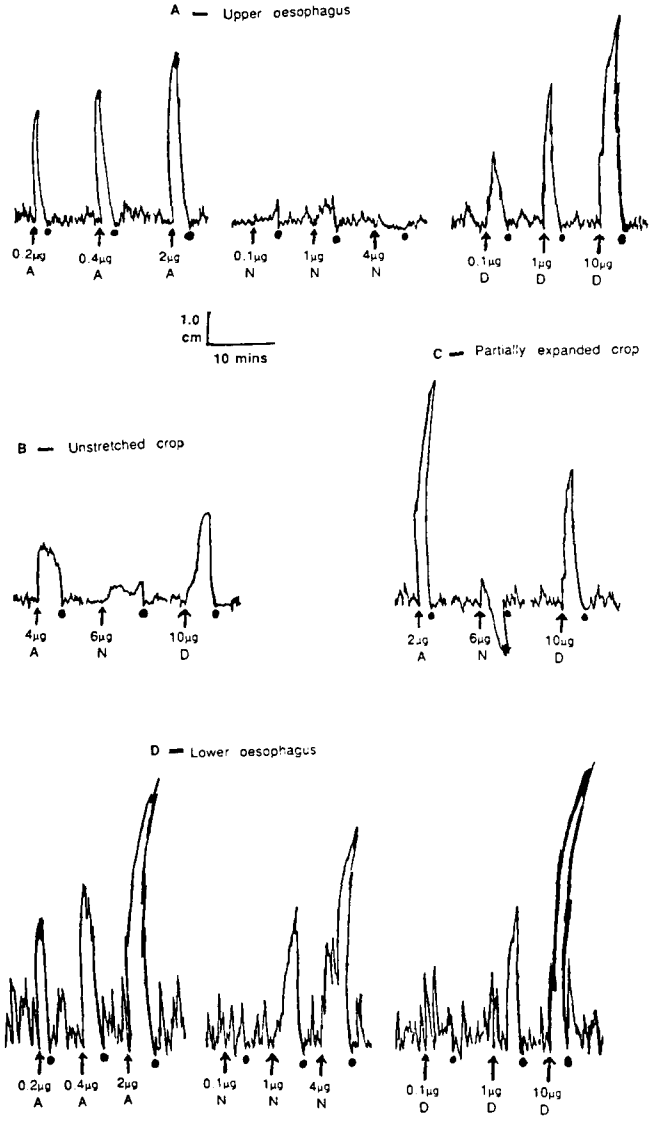


FIG. 1. Representative responses (n = 6) of various gastrointestinal segments to acetylcholine (A), noradrenaline (N) or dopamine (D) added in doses (final bath concentrations in g $mL^{-1}$) indicated for each drug at the arrows, followed by washing (●) with several changes of fresh physiological solution. A, Upper oesophagus; B, unstretched (normal) crop; C, partially expanded crop; D, lower oesophagus. Deflections recorded above the baseline denote contractions while those below the baseline represent relaxations, both expressed in centimetres.

## Results and Discussion

The results of this study are summarized in Figs 1–3.

The gastrointestinal tract from all three strains of chicks used in this study exhibited spontaneous rhythmic activity. This observation is consistent with the known physiology of the gastrointestinal tract (Rang & Dale 1991). The finding that acetylcholine contracted all segments of the tract is also consistent with its physiology since this organ is innervated by parasympathetic nerves and contracts in response to parasympathetic stimulation (Rang & Dale 1991). However, different segments showed variations in sensitivity to acetylcholine, as noted in this study.

Stimulation of sympathetic nerves should cause relaxation (Rang & Dale 1991) and noradrenaline would be expected to relax all segments. However, results from this study showed that noradrenaline contracted most preparations from the crop and lower oesophagus of chicks. Studies involving the lower oesophagus showed that noradrenaline-induced contraction of the lower oesophagus was mediated by stimulation of α-adrenoceptors since the contractions were abolished by prazosin. In the presence of prazosin, noradrenaline relaxed the lower oesophagus. This observation, together with the finding that isoprenaline caused relaxation of the lower oesophagus which was antagonized by propranolol, show that stimulation of β-adrenoceptors relaxes the lower oesophagus. Thus, stimulation of α-adrenoceptors contracts,

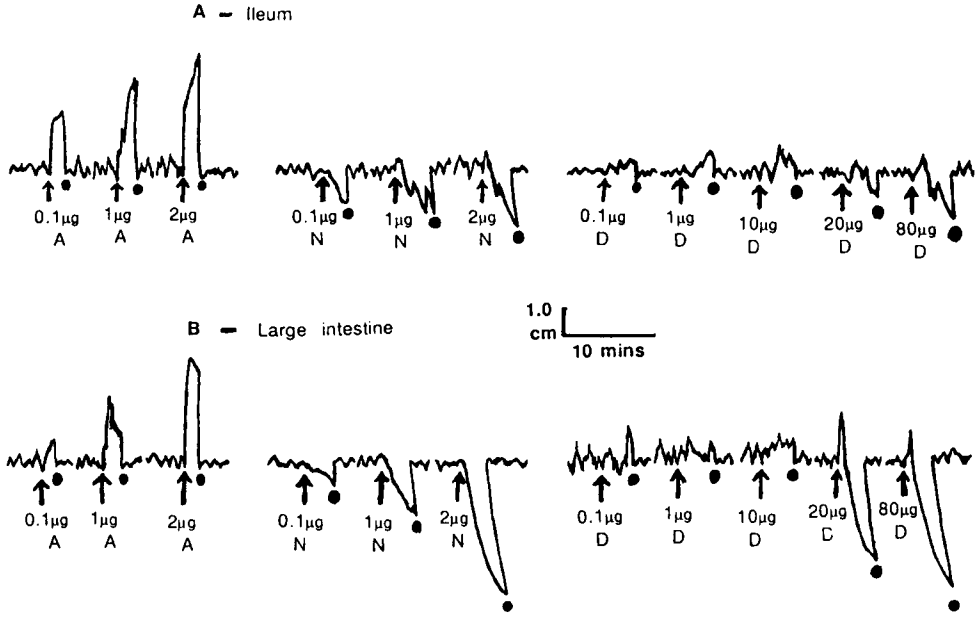


FIG. 2. Representative responses (n = 6) of various gastrointestinal segments to acetylcholine (A), noradrenaline (N) or dopamine (D) added in doses (final bath concentrations in g $mL^{-1}$) indicated for each drug at the arrows, followed by washing (●) with several changes of fresh physiological solution. A, ileum; B, large intestine. Deflections recorded above the baseline denote contractions while those below the baseline represent relaxations, both expressed in centimetres.

while stimulation of β-adrenoceptors relaxes the lower oesophagus of chicks.

Another notable observation in this study relates to results for the crop, a structure found in chicks but not in mammals. The normal crop was found to be less responsive to drugs than the partially expanded crop. More interestingly, noradrenaline caused weak contractions of the crop but relaxed the partially expanded crop. The reason for such a variation in response to noradrenaline was not investigated but could be due to relative differences in contribution of α- and β-adrenergic receptors mediating its effects in this tissue.

Relaxations of the duodenum, ileum, large intestine and caecum induced by noradrenaline are consistent with the known physiology of sympathetic innervation of such segments of the gastrointestinal tract (Rang & Dale 1991).

Dopamine contracted the upper oesophagus, normal or partially expanded crop and the lower oesophagus. This pattern of effects is similar to that produced by acetylcholine but differs remarkably from the actions of noradrenaline in these preparations. Such actions of dopamine and the possible mechanism by which dopamine could produce such actions do not seem to have been reported and have been investigated in the present study. Results from the present study showed that the effects of dopamine on the duodenum, ileum, large intestine and caecum differed from those of acetylcholine although they resembled those of noradrenaline. A notable difference between the actions of dopamine and noradrenaline in these segments was the contractions seen with low dopamine concentrations, or preceding dopamine-induced relaxations (Fig. 2). The possibility that dopamine could produce some of its effects in a similar fashion to noradrenaline have been investigated in a separate study using the isolated expansor secundariorum muscle, a smooth muscle in the wing of chicks wholly innervated by noradrenergic nerves (Lot & Bennett 1982).

Contraction of the lower oesophagus caused by acetylcholine was antagonized by atropine, a known muscarinic receptor antagonist. This indicates that muscarinic receptors mediate contraction of the lower oesophagus induced by acetylcholine, as previously reported (Lot & Bennett 1982; Lot 1992; Lot & Udoh 1992). By means of specific antagonists, the presence of histamine ($H_1$), α-adrenergic and 5-HT-ergic receptors were also identified and their stimulation caused contraction of the lower oesophagus. Since dopamine caused contraction of the lower oesophagus, the possibility of its acting through one of these receptors was investigated using the specific antagonists for these various agonists. Results from the present study showed that LSD antagonized the contraction produced by dopamine while atropine, mepyramine and prazosin had no such effect, indicating that 5-HT-ergic receptors mediate contraction of the lower oesophagus induced by dopamine. The finding with isoprenaline and propranolol that stimulation of β-adrenergic receptors relaxes the lower oesophagus indicates that dopamine is unlikely to act through those receptors, and this was confirmed by the lack of antagonistic effect of propranolol on dopamine-induced contraction of this preparation.

Results from the present study showed that repeated administration of a large concentration of dopamine caused tachyphylaxis in the lower oesophagus. This observation suggests that dopamine contracts the lower oesophagus by releasing 5-HT, rather than by direct stimulation of 5-HT-

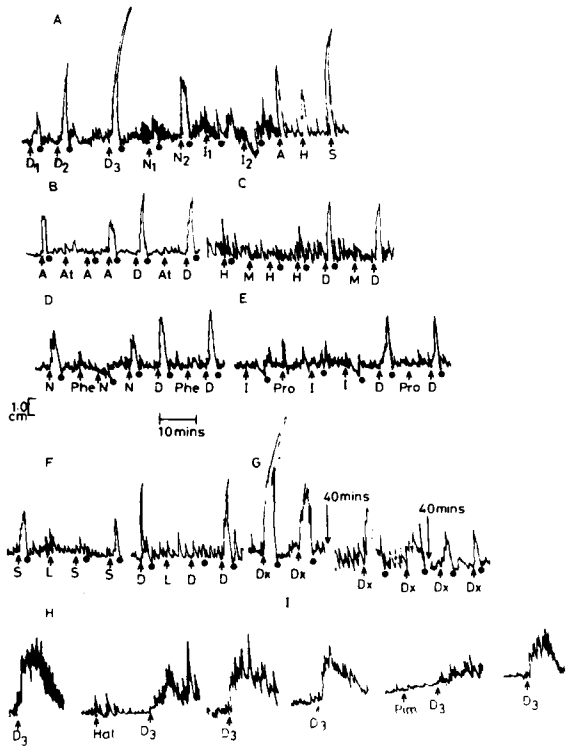


FIG. 3. Representative responses (n = 6) of the lower oesophagus to drugs added at the arrows, followed by washing (●) with several changes of fresh physiological solution. Antagonists were administered 5 min before agonists. Deflections recorded above the baseline denote contractions while those below the baseline represent relaxations (both expressed in centimetres). A; $D_1 = 3$ μg mL$^{-1}$ dopamine, $D_2 = 5$ μg mL$^{-1}$ dopamine, $D_3 = 10$ μg mL$^{-1}$ dopamine, $N_1 = 3$ μg mL$^{-1}$ noradrenaline, $N_2 = 5$ μg mL$^{-1}$ noradrenaline, $I_1 = 0{\cdot}5$ μg mL$^{-1}$ isoprenaline, $I_2 = 1$ μg mL$^{-1}$ isoprenaline, A = 1 μg mL$^{-1}$ acetylcholine, H = 3 μg mL$^{-1}$ histamine, S = 0·5 μg mL 5-HT. B; A = 1 μg mL$^{-1}$ acetylcholine, At = 10 ng mL$^{-1}$ atropine, D = 5 μg mL$^{-1}$ dopamine. C; H = 2 μg mL$^{-1}$ histamine, M = 0·1 μg mL$^{-1}$ mepyramine, D = 5 μg mL$^{-1}$ dopamine. D; N = 3 μg mL$^{-1}$ noradrenaline, Phe = 0·5 μg mL$^{-1}$ phentolamine, D = 5 μg mL$^{-1}$ dopamine. E; I = 0·5 μg mL$^{-1}$ isoprenaline, Pro = 0·5 μg mL$^{-1}$ propranolol, D = 5 μg mL$^{-1}$ dopamine. F; S = 50 ng mL$^{-1}$ 5-HT, L = 0·1 μg mL$^{-1}$ LSD, D = 5 μg mL$^{-1}$ dopamine. G; Dx = 20 μg mL$^{-1}$ dopamine. H; $D_3 = 10$ μg mL$^{-1}$ dopamine, Hal = 5 μg mL$^{-1}$ haloperidol. I; $D_3 = 10$ μg mL$^{-1}$ dopamine, Pim = 5 μg mL$^{-1}$ pimozide.

ergic receptors. This suggestion is based on observations that indirectly-acting sympathomimetic agents cause tachyphylaxis by depleting transmitter stores at the nerve terminal (Rang & Dale 1991).

In concentrations shown to be selective for dopamine, moderate doses of haloperidol and pimozide partially antagonized contraction of the lower oesophagus induced by dopamine. This raises the interesting possibility that stimulation of specific dopaminergic receptors could contribute to contraction of the lower oesophagus induced by dopamine, although results from the present study would tend to suggest that the relative contribution of stimulating such receptors to the overall action of dopamine would be less than stimulation of 5-HT-ergic receptors.

In conclusion, the present study has shown that dopamine contracts the upper and lower oesophagus as well as the crop, but relaxes the duodenum, ileum, large intestine and caecum from chicks. Contraction of the lower oesophagus by dopamine appeared to be mediated largely by 5-HT release, and also by stimulation of dopaminergic receptors in that preparation.

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