*J. Reprod. Fert.* (1968) **17**, 95–100

# OVIDUCT CIRCULAR MUSCLE RESPONSE TO DRUGS RELATED TO THE AUTONOMIC NERVOUS SYSTEM

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(*Received 30th September* 1967, *accepted 6th March* 1968)

**Summary.** The influence of various autonomic drugs on the circular muscle of the oviduct was studied. The changes in oviduct motility patterns were measured in anaesthetized Dutch Belted rabbits with a perfusion apparatus and pressure transducer. Intravenous noradrenaline (1 to 4 μg/kg) and adrenaline (2·5 to 7·5 μg/kg) resulted in a sustained contraction of the oviduct followed by contraction at a higher tone. Isoprenaline (1 to 4 μg/kg) caused a relaxation of the oviduct musculature. Phenoxybenzamine (3 mg/kg subcutaneously) blocked the action of adrenaline for at least 4 hr. Propranolol blocked the action of isoprenaline for 1 to 2 hr. The results of administering acetylcholine and scopolamine were inconclusive.

## INTRODUCTION

Sympathetic innervation of the oviduct is through the hypogastric nerves (Langley & Anderson, 1894, 1895; Brundin, 1965). Rosenblum & Stein (1966) were unable to demonstrate any pharmacological evidence for the presence of cholinergic ganglia in the human oviduct *in vitro*. They did, however, note the presence of alpha adrenergic-constrictor beta adrenergic-dilator and cholinergic-constrictor receptors in the circular muscle component of the oviduct. Kok (1927, as cited by Brundin, 1965) observed that the rabbit oviduct contracted when the sacral parasympathetic nerves ($S_1$–$S_{111}$) were stimulated, while stimulation of the sympathetic nerves (hypogastric) generally had a relaxing effect on the musculature of the same oviduct. Brundin (1964a, 1965) found that electrical stimulation of the hypogastric nerves immediately below the inferior mesenteric ganglia increased the pressure required to open the isthmus and the perfusion pressure of the ampulla-infundibulum in the rabbit oviduct. The pressure required to open the isthmus was not lowered by reserpine pre-treatment, or after pentamethonium. Blocking of the alpha adrenergic-receptors by phentolamine decreased the opening pressure. Reserpine pre-treatment or phentolamine administration decreased or abolished the stimulatory response resulting from electrical stimulation of the hypogastric nerves. Brundin and his co-workers demonstrated histologically that the

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number of adrenergic nerve terminals in the musculature increased progressively from the ovarian to the uterine end of the tube in both rabbit and human oviducts (Brundin 1964b, 1965; Brundin & Wirsén, 1964b).

Davids & Bender (1940a) noted that in the rabbit acetylcholine generally had an inhibitory effect on the oviduct which was directly antagonistic to the motor action of adrenaline. Sandberg, Ingelman-Sundberg, Lindgren & Ryden (1960) found that the longitudinal musculature responded similarly to acetylcholine, adrenaline and noradrenaline. A more comprehensive review of pertinent literature appears in Brundin (1965).

The research presented here was conducted to determine the influence of several drugs related to the autonomic nervous system on the circular muscle component of the isthmus of the rabbit oviduct.

## MATERIALS AND METHODS

Virgin Dutch Belted females mated 24 hr previously were used in this study. The rabbits were anaesthetized with sodium pentobarbitone and the circular muscle activity of the oviduct measured. A perfusion apparatus similar to the one described by Brundin (1965) was used to measure circular muscle response. The pressure in the system was controlled by a vessel of mercury and flow rate by a piece of thick-walled glass capillary tubing which had been heated and drawn out so as to decrease the size of the bore. The flow rate of the apparatus was approximately 0·5 ml of 0·9% NaCl/min at a pressure of 140 mm of mercury. Pressure fluctuations in the perfusion system were measured with a model 267 B Sanborn pressure transducer attached to a Sanborn four channel recorder (Model 964). A polyethylene cannula (O.D. 1·22 mm, I.D. 0·76 mm) connected the perfusion apparatus to the oviduct, which was exposed by a mid-ventral incision. A small opening was cut in the oviduct about midway between the uterine and ovarian ends through which the cannula was inserted and sutured in place. A piece of polyethylene tubing (O.D approximately 5 mm) was inserted through a slit in the uterus and secured with one end near the tubo-uterine junction. The other end was left free to allow removal of saline after it was perfused through the oviduct. With this apparatus, muscular activity was measured as a change in resistance to fluid flow. When the muscle relaxed, the pressure at the level of the transducer was reduced; when contraction occurred the opposite result was observed.

Drugs given intravenously were administered through a polyethylene cannula (O.D. 2·08 mm, I.D. 1·57 mm) in the jugular vein. The jugular cannulae were calculated to have a dead space of between 0·5 and 0·6 ml. Drugs were injected through the cannula in amounts of less than 0·5 ml (drug plus carrier) with a syringe equipped with a three-way stopcock and a volume of 0·9% NaCl equivalent to the measured dead space of the cannula was injected immediately after the drug. Drugs were also given subcutaneously at various sites on the body.

Blood pressure and heart rate were determined with a carotid cannula (O.D. 2·08 mm, I.D. 1·57 mm) attached to a pressure transducer and the recorder. These measurements permitted a comparison of the cardiovascular

response with the oviduct response to the various drugs. Heparin (1000 units) was given immediately following completion of the surgical procedure.

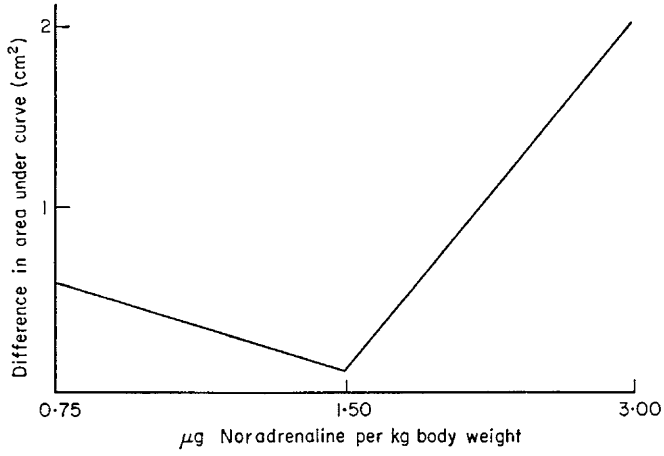
Drugs were administered at various levels to establish dose-response curves. Noradrenaline (L-arterenol hydrochloride) was given at the rate of 0·75, 1·50 and 3·00 μg/kg by way of the jugular cannula. Adrenaline (Wolins Pharmaceutical Corporations) was given intravenously at the levels of 2·5, 5·0 and 7·5 μg/kg of body weight. Ten minutes were allowed between each injection of drug. All values are given as actual amounts of the active compound.

After the response to adrenaline had been determined, 3 mg/kg phenoxybenzamine (Smith, Kline and French Laboratories) was administered. At 1-hr intervals after subcutaneous administration of phenoxybenzamine the block was challenged by giving adrenaline as in the control. Similarly, propranolol (Ayerst Laboratories) was given at the level of 7 mg/kg subcutaneously and challenged with isoprenaline. Scopolamine hydrobromide (56 mg/kg of scopolamine) was given subcutaneously and challenged with acetylcholine.

The graphic records were analysed by measuring the area under the curve for 3 min immediately before and after administration of the challenging drugs. The difference in the area under the curve as a result of the drug administration was plotted as a dose–response curve on semi-log paper. The procedure of taking the area under the curve was shown by Stander (1966) to give an accurate measurement of response to drugs in uterine muscle studies.

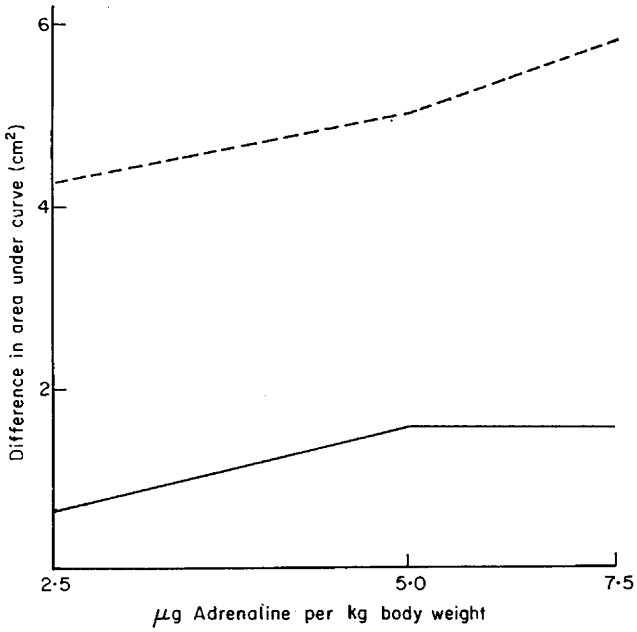
## RESULTS

The intravenous injection of either noradrenaline or adrenaline altered the pattern of oviduct muscular contractions. Both drugs caused sustained contraction of the oviduct followed by rhythmic contractions with an elevated



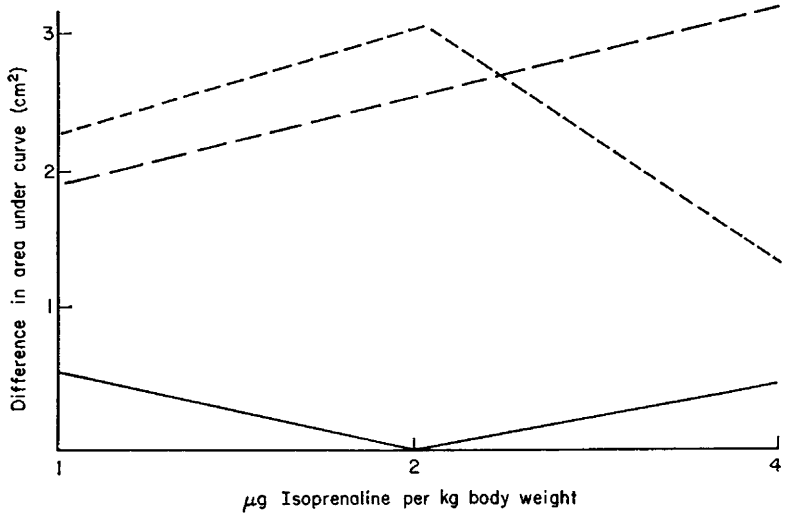

TEXT-FIG. 1. Changes in area under curve for oviduct tracings caused by noradrenaline administration.

base line. The pattern changed almost instantaneously after injection and returned to normal in less than 2 min. With larger doses, a longer time was required for oviduct motility to return to normal. When the altered oviduct




TEXT-FIG. 2. Changes in area under curve for oviduct tracings caused by adrenaline administration before and after phenoxybenzamine administration. — — — —, 4 hr after phenoxybenzamine; ——, control.

motility pattern was compared to that immediately before the injection, the area under the curve was found to have increased at all drug levels used (Text-figs. 1 and 2). Adrenaline at the levels used resulted in greater changes




TEXT-FIG. 3. Changes in area under curve for oviduct tracings caused by isoprenaline administration before and after propranolol administration. ——, 1 hr after propanolol; - - - - -, 2 hr after propanolol; — — — , control.

than noradrenaline. A single subcutaneous injection of phenoxybenzamine (3 mg/kg) reduced the action of adrenaline 4 hr after its administration. Twenty minutes to ½ hr were required to establish a block with phenoxybenzamine.

Isoprenaline reduced the area under the curve (Text-fig. 3). The pattern of oviduct muscular contraction resulting from isoprenaline injection was one of reduced tone with only small contractions. The magnitude was reduced as the amount of drug was increased. The administration of propranolol (7 mg/kg) reduced this response for a period of 1 to 2 hr (Text-fig. 3).

Acetylcholine caused a slight increase in the area under the curve. Although sufficient drug was used to reduce blood pressure, no conclusive alterations in the patterns of muscle contractions could be seen. The slight increase in tone noticed occasionally may have been due to adrenal medullary discharge of adrenaline. Scopolamine (56 mg/kg) resulted in very little change in muscular activity. It appeared that scopolamine increased the sensitivity of the oviduct to acetylcholine. Scopolamine, however, slightly blocked the action of acetylcholine on the cardiovascular system.

## DISCUSSION

The results of this experiment indicate that the circular muscle of the oviduct responds to adrenergic stimulation. The alpha adrenergic receptors appear to be stimulatory while the beta receptors are inhibitory. These results are in agreement with those of Ahlquist (1948) and Ahlquist & Levy (1959), indicating that the circular, smooth muscle of the oviduct reacts as do most smooth muscles of the body. Rosenblum & Stein (1966), working with isolated human oviducts, noted similar responses. In the uterus of the guinea-pig alpha receptors have been reported to be stimulatory while beta were dilatory (Davidson & Ikoku, 1966). Brundin (1965) noted that the alpha-blocking agent, phentolamine, decreased the pressure necessary for perfusion of the oviduct. Observations in the present study show that the alpha-blocking agent, phenoxybenzamine, reduces the tone of the oviduct and this is in agreement with the findings of Brundin (1965).

Although both alpha and beta receptors appear to be present in the rabbit oviduct, the response obtained by administration of adrenaline indicates that the alpha receptors predominate.

The results obtained after acetylcholine and scopolamine treatment were inconclusive. Parasympathetic stimulation caused contraction of the rabbit (Kok, 1927, as cited by Brundin, 1965) and human oviduct (Sandberg *et al.*, 1960). Acetylcholine, on the other hand, had an inhibitory effect on the rabbit oviduct (Davids & Bender, 1940b). The conflicting reports suggest a neuroendocrine relationship. An interplay of steroid hormones with the autonomic nervous system in the rabbit uterus was reported by Miller & Marshall (1965). They noted that adrenergic receptors in the myometrium of oestrogen-treated rabbits were predominantly excitatory while those in the uterus of progesterone-treated animals were inhibitory.

ACKNOWLEDGMENTS

The work reported here was submitted in part by the senior author to the Graduate School, University of Massachusetts, in partial fulfilment of the Ph.D. degree, and was supported by the National Institute of Health Grant HD 00745. The authors wish to express their appreciation to Ayerst Laboratories for propranolol and to Smith, Kline and French for the phenoxybenzamine.

REFERENCES

AHLQUIST, R. P. (1948) A study of the adrenergic receptors. *Am. J. Physiol.* **153,** 586.

AHLQUIST, R. P. & LEVY, B. (1959) Adrenergic receptive mechanism of the canine ileum. *J. Pharmac. exp. Ther.* **127,** 146.

BRUNDIN, J. (1964a) A functional block in the isthmus of the rabbit Fallopian tube. *Acta physiol. scand.* **60,** 295.

BRUNDIN, J. (1964b) An occlusive mechanism in the Fallopian tube of the rabbit. *Acta physiol. scand.* **61,** 219.

BRUNDIN, J. (1965) Distribution and function of adrenergic nerves in the rabbit Fallopian tube. *Acta physiol. scand.* **66,** Suppl. 259.

BRUNDIN, J. & WIRSÉN, C. (1964a) The distribution of adrenergic nerve terminals in the rabbit oviduct. *Acta physiol. scand.* **61,** 203.

BRUNDIN, K. & WIRSÉN, C. (1964b) Adrenergic nerve terminals in the human Fallopian tube examined by fluorescence microscopy. *Acta physiol. scand.* **61,** 505.

DAVIDS, A. M. & BENDER, M. B. (1940a) Effects of adrenalin on tubal contractions of the rabbit in relation to the sex hormones (study *in vivo* by Rubin method). *Am. J. Physiol.* **129,** 259.

DAVIDS, A. M. & BENDER, M. B. (1940b) The relaxation of acetylcholine on the oviduct of the rabbit in relation to hormonal status. *Am. J. Physiol.* **131,** 240.

DAVIDSON, W. J. & IKOKU, C. (1966) The adrenergic receptors in the guinea pig uterus. *Can. J. Physiol. Pharmac.* **44,** 491.

KOK, F. (1927) Über die Versorgung der Fallopiochen Tube mit motorischen Newen. *Arch. Gynaek.* **130,** 173. (From Brundin, 1965.)

LANGLEY, J. N. & ANDERSON, H. K. (1894) The constituents of hypogastric nerves. *J. Physiol., Lond.* **17,** 177.

LANGLEY, J. N. & ANDERSON, H. K. (1895) The innervation of the pelvic and adjoining viscera. Part IV. The internal generative organs. Part V. Position of the nerve cells on the course of the efferent nerve fibers. *J. Physiol., Lond.* **19,** 71.

MILLER, H. D. & MARSHALL, J. M. (1965) Uterine response to nerve stimulation; relation to hormonal status and catecholamines. *Am. J. Physiol.* **209,** 859.

ROSENBLUM, I. & STEIN, A. A. (1966) Autonomic responses of the circular muscles of the isolated human Fallopian tube. *Am. J. Physiol.* **210,** 1127.

SANDBERG, F., INGELMAN-SUNDBERG, A., LINDGREN, L. & RYDEN, G. (1960) *In vitro* studies of the motility of the human Fallopian tube. Part 1. The effects of acetylcholine, adrenaline, noradrenaline and oxytocin on the spontaneous motility. *Acta obstet. gynec. scand.* **39,** 506.

STANDER, R. W. (1966) An approach to quantitative analysis of intrauterine pressure data. *Obstet. Gynec., N.Y.* **27,** 110.