Responses of the monkey oviduct to transmural electrical stimulation and to drugs

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In monkeys, as in man, the time required for ovum transport through the oviduct is about 3 days (Eddy, Garcia, Kraemer & Pauerstein, 1976). This period appears essential for normal fertility because eggs passing too quickly or too slowly through the oviduct fail to implant (Bennett, 1974). Although transport through the ampulla may be mediated by cilia (Blandau & Verdugo, 1976), the isthmus is comparatively muscular and well innervated and may delay ovum transport by a sphincter-like action. Prostaglandins and catecholamines are known to alter the muscular activity of human and rabbit oviducts and it is possible that changes in the levels of these drugs, or in the sensitivity of the tissues to them, may control egg transport (Hodgson & Eddy, 1975; Spilman & Harper, 1975). In the present study the contractile responses of the monkey oviduct to various drugs and to transmural electrical stimulation have been examined in the hope of increasing understanding of the regulation of ovum transport in this species.

Tissues were obtained from mature female crab-eating macaques (*Macaca fascicularis*). Uteri with their attached oviducts were removed under halothane anaesthesia and were placed in cold Krebs solution. Each oviduct was then separated from the uterus and the attached connective tissue and ligaments dissected away. One 4-mm and two 2-mm lengths of tube were then obtained from both the isthmus and the ampullary regions. The shorter lengths were connected together with thread in the form of rings for recording of circular muscle activity; the longer sections were suspended longitudinally. Both types of preparation were suspended in Krebs solution at 37°C under a tension of 490 or 980 dyn. The Krebs solution consisted of (mM): Na⁺, 139; K⁺, 5.4; Ca²⁺, 2.5; Mg²⁺, 1.2; Cl⁻, 129; HCO₃⁻, 22; H₂PO₄⁻, 1.2; D-glucose, 11.1, and was bubbled with 95% O₂ + 5% CO₂. During transmural electrical stimulation, tissues were continuously superfused with Krebs solution at 1–2 ml/min. The medium had a pH of 7.40 ± 0.02. Tension was recorded by using Grass FT03C transducers and displayed on Dynograph or Grass pen recorders.

Compounds were added to the organ baths, 5 or 10 ml volume, as small (10–50 µl) amounts of stock solutions. The baths were washed out with fresh Krebs solution when the tissues had produced a maximal response. Transmural electrical stimulation was generally for 60 sec and consisted of biphasic pulses, of 1 msec duration and supramaximal voltage, delivered at 2 to 29 Hz. Tissues were allowed to equilibrate in Krebs solution at 37°C for 30 min before electrical stimulation or addition of drugs.

The hormonal status of each animal was determined by histological examination of the uterus and oviduct.

All the preparations were spontaneously active. Several types of activity were seen. Some preparations showed rapid repetitive spike-like contractions at frequencies of up to 10/min. In others, large regular sustained contractions were seen at intervals of from 1 to several minutes. Frequently, both forms of rhythm were seen in the same preparation. In a few tissues the activity was irregular, while in others activity consisted of bursts of high-frequency contractions occurring at intervals of 5–10 min, the tissue being quiescent in the intervening periods. No particular form of spontaneous activity was characteristic of any hormonal state or portion of the oviduct.

The responses to transmural electrical stimulation of oviductal preparations from 12 monkeys were tested. It can be seen from the results in Table 1 that a response was produced in about 50% of the trials. The responsive tissues showed a threshold for response at about 8 Hz. In the circular and

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Table 1. The responses of different parts of the oviduct of monkeys to transmural electrical stimulation at 20 Hz

	Ampulla		Isthmus	
	Longitudinal	Circular	Longitudinal	Circular
No response	5	8	6	7
Contraction	7	4	3	5
Relaxation	0	0	3	0

longitudinal muscle of the ampulla and in the circular muscle of the isthmus the response was invariably a contraction. The longitudinal isthmus, however, contracted or relaxed with equal frequency. In no case was the response very great and was often obscured by the spontaneous activity of the tissue. Preparations from monkeys in the luteal phase were more sensitive than those from animals in the follicular phase of the cycle. In two of the three preparations in which the longitudinal isthmus relaxed in response to transmural stimulation, propranolol (3.9×10^{-6} M) converted the relaxation to a contraction. When phenolamine (10^{-5} M) was tested it abolished the contractile responses of all types of oviductal musculature.

The effects of various compounds on the contractility of oviducts (number tested shown in parentheses) were examined: (–)-noradrenaline (11), prostaglandin F-2 α (11), acetylcholine (6), 5-hydroxytryptamine (3), prostaglandin E-2 (6), and histamine (12). All sections of the oviduct at all stages in the menstrual cycle were remarkably insensitive to all drugs, except histamine. Histamine, at concentrations greater than about 10^{-6} M, always induced a prolonged contraction but the muscle rapidly developed tachyphylaxis. (–)-Noradrenaline at concentrations of up to 3×10^{-4} M resulted in contraction or increased spontaneous activity, but even with the highest doses used it was sometimes ineffective. Acetylcholine (3.4×10^{-4} M) had no action except for one instance of a contraction in a progesterone-dominant oviduct which was also unusually sensitive to other drugs. Prostaglandin F-2 α (1.4×10^{-5} M) generally caused contractions but was not always able to elicit a response. PGE-2, in doses of up to 2.8×10^{-5} M, was generally without effect, although there was sometimes a diminution in the rate and amplitude of the spontaneous contractions. 5-Hydroxytryptamine (3.6×10^{-5} M) had virtually no effect, eliciting small contractions from some tissues. The responses of preparations from one oviduct to transmural electrical stimulation and various compounds are illustrated in Text-fig. 1. The similarity in the responses to transmural electrical stimulation and to exogenous noradrenaline was seen in all other tissues that responded to these treatments. Because of the response of the oviduct tissue to histamine, the effects of mepyramine on spontaneous activity were tested: a dose of 8.8×10^{-5} M abolished the response to a test dose of histamine, but was without effect on the spontaneous activity or tone.

The main finding of this study is the relative insensitivity of the monkey oviduct to transmural electrical stimulation and to drugs. In this respect, it differs markedly from the responses of rabbit and human oviducts. The rabbit oviduct always responded *in vitro* with a sustained contraction to transmural electrical stimulation and to noradrenaline (Johns & Paton, 1975a, b). By contrast, the responses of the human oviduct *in vitro* appear to be markedly dependent on hormonal status; in the luteal phase, transmural electrical stimulation and noradrenaline are inhibitory, whereas responses are more variable in the follicular phase (Molnar, Johns, Paton, Daniel & Beck, 1976; Moawad, Hedqvist & Kim, 1976). Similarly, the effects of prostaglandins on the monkey oviduct appear to be much less marked than those reported in studies on rabbit and human oviducts (Spilman & Harper, 1975). The monkey oviduct may not, therefore, be a good model for the human oviduct as its pharmacological characteristics differ significantly.

The relative insensitivity of the monkey oviduct to transmural electrical stimulation and to noradrenaline and prostaglandins suggest that the adrenergic innervation and generation of prostaglandins in the oviduct do not play a major role in the regulation of ovum transport in this species. The present study of responses *in vitro* may not accurately reflect responses *in vivo*. Ultrastructural

Text-fig. 1. The responses of monkey oviductal preparations (in the early follicular phase) to transmural electrical stimulation (at 20 Hz) and to various compounds: NA, 5.9×10^{-5} M(-)-noradrenaline; ACh, 6.8×10^{-5} M-acetylcholine; 5HT, 5.7×10^{-5} M-5-hydroxytryptamine; PGF-2 α , 2.8×10^{-5} M prostaglandin F-2 α ; PGE-2, 2.8×10^{-5} M-prostaglandin E-2; Hist, 9×10^{-5} M-histamine. The horizontal bars indicate the duration of electrical or chemical stimulation. IL = longitudinal isthmus muscle; IC = circular isthmus muscle; AL = longitudinal ampullary muscle; AC = circular ampullary muscle.

studies of the monkey oviduct have shown that only a small percentage of smooth muscle cells in the monkey oviduct are innervated by adrenergic nerves (J. H. Widdicombe, unpublished results), in keeping with the poor response to transmural electrical stimulation. Sympathectomy has minimal effects on ovum transport in the rabbit (Pauerstein, Hodgson, Fremming & Martin, 1974) and on the fertility of female mice (Johns, Chlumecky, Cottle & Paton, 1975), providing more direct evidence against a major role for adrenergic innervation of the oviduct in these species.

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