# Chapter I

## Introduction

The fallopian tubes, or oviducts, a pair of open-ended tubes connecting the ovaries with the uterus, usually divided into four regions; the uterotubal junction, isthmus, ampulla and infundibulum are intimately involved in ovum transport. How ovum transport is regulated can be hyphothesized. The transport of ova through the oviduct may involve a number of mechanisms; muscular contractions of the tubal wall, epithelial ciliary activity, and the flow of oviduct secretions. (Harper, 1961; Halbert, Tam, and Blandua, 1976). To elucidate the mechanisms involved in ovum transport, roles of ciliary activity, luminal fluid dynamics and smooth muscle contractility have been investigated. Evidence previously obtained supports the view that ovum transport is mainly regulated by peristaltic contractions-cells (Coutinho, Maia, and Mattos, 1975; Croxatto and Ortiz, 1975).

The regulation of ovum transport is extremely important since the success of the reproductive process is dependent upon implantation of the ovum occurring at the right stages of endometrial maturation and of embryonic development.

Drugs or agents such as hormones, neurotransmitters, which accelerate or retard ovum transport *via* tubal muscular activities, disturb this delicate balance and prevent uterine implantation. For example, in the rabbit (Nozaki and Ito, 1987), guinea-pig and hamster (Greenwald, 1968)

administration of large doses of estrogen before ovulation causes a marked delay in ovum transport with most ova being retained in the ampulla, or at the ampulla-isthmic junction. Whereas the administration of smaller doses of estrogen at suitable time causes accelerated ovum transport in the mouse, rabbit, rat, guinea-pig and hamster. The administration of progesterone before ovulation causes acceleration of ovum transport in rabbits (Greenwald, 1968).

These findings suggest that any chemicals which accelerate or retard ovum transport would prevent implantation and pregnancy in women and hence would have potential as contraceptives.

The oviduct is dually innervated, receiving nerves from both the sympathetic and parasympathetic divisions of the autonomic nervous system. Paton et al., (1978) suggested that human oviduct contained a plexus analogous to Meissner's plexus of the intestine. The distribution of nerves within the tube determined by traditional heavy metal staining methods is well described, the nerve fibres follow the large subserosa blood vessels and then branch down smaller blood vessels to produce a plexus within the muscle layers. It seems fair to say, however, that the cholinergic innervation is slight when compared to the adrenergic, and norepinephrine (NE) is the predominant aminergic transmitter in the oviducts of the guinea-pig, rabbit, and human (Marshall, 1981).

Fluorescent histochemical technique for biogenic amines has demonstrated a dense adrenergic innervation to the muscle of ampulla and isthmus of a number of species, including man (Paton et al, 1978; Hoffman et

al., 1981; Bulat, Kannan, and Garfield, 1989). Pharmacological investigations have demonstrated the presence of alpha-excitatory and beta-inhibitory adrenoceptors in oviductal smooth muscle (Rosenblum and Stein, 1966; Nakanishi and Wood, 1967; Spilman and Harper, 1974; Paton et al., 1978; Borda et al., 1979; Hoffman et al., 1981; Maltier and Legrand, 1985). The adrenergic transmission could in turn be regulated by the prevailing hormonal dominance. It has been proposed that estrogen enhances alpha-adrenoceptor activity and thus constriction of the tube, and that by the production of progesterone potentiates beta-adrenoceptor activity with a consequent reduction in constriction of the tube (Hoffman et al., 1981; Nozaki and Ito, 1987; Bennett et al., 1988).

In the oviducts of all species, including the human, activation of alpha- and beta-adrenoceptors by NE resulted in contraction and inhibition of contractility of smooth muscle, respectively (Sandberg et al., 1960; Diamond and Marshall, 1969; Magaribuchi and Osa, 1971; Spilman and Harper, 1974; Ruckebusch and Pichot, 1975; Molnar et al., 1976; Chow and Marshall, 1981; Bulbring and Tomita, 1987).

The presence of cholinergic receptors in human fallopian tube muscles has been demonstrated with methacholine which has been blocked by atropine (Rosenblum and Stein, 1966). Acetylcholine administration, resulting in contraction of smooth muscle has also been reported (Sandberg et al., 1960).

The other possible neurotransmitter which has been reported to play a role on contractility of the fallopian tube, is GABA (gamma-aminobutyric

acid) (Erdo et al., 1984). Assuming a possible neurotransmitter function of GABA in the fallopian tube, it seems conceivable that-like the autonomic neurotransmitters NE and ACh-GABA may modulate the spontaneous motility of the oviductal smooth muscle.

In experiments with human tissues, lines of evidence have indentified GABA and high density of specific GABA receptor binding sites in the human ovary, uterus and fallopian tube. (Erdo et al., 1983; Erdo and Laszlo, 1984; Erdo, Villanyi, and Laszlo, 1989). These findings suggest a possible role of GABA in female genital tract.

The effects of GABA and related compounds were examined on longitudinal and circular muscle preparations isolated from oviducts of virgin rabbits. GABA and baclofen stimulated spontaneous motility in both preparations. This action could not be antagonized by either bicuculline, phentolamine, atropine, or tetrodotoxin, whereas muscimol was virtually ineffective in stimulating spontaneous motility. The results indicate the presence of GABA-B receptors in the rabbit oviductal musculature which may mediate the contractile response. (Erdo et al., 1984).

Fernandez, Orensanz and de Ceballos (1984) reported that rat oviduct did not respond to GABA, whereas ACh-induced contraction in this tissue was augmented by GABA and its agonist, muscimol. This augmentation was antagonized by bicuculline. The mechanism for GABA-induced enhancement of ACh stimulated contractions may not involve increase in ACh release, but rather due to a postsynaptic modulatory effect mediated through GABA-A receptors.

Erdo et al. (1983), reported that the properties of [$^3$H]-GABA binding sites in the human fallopian tube resemble those of GABA-A receptors. In 1985, Erdo et al., also demonstrated a remarkable density of high-affinity and specific GABA binding sites in membranes of the human term placenta. These binding sites show the properties of a GABA-A receptors. However, there is no documentation of GABA action on motility of human fallopian tube. The principal aim of the present study is to elucidate whether GABA may play any physiological role on fallopian tube smooth muscle activities, and if so, GABA-A or GABA-B receptor, is responsible for contractility of the tube. In addition, to study the contractility of this organ resulted either from GABA effects directly as transmitter itself on smooth muscle or indirect by acting as co-regulators with the autonomic neurotransmitter, NE and ACh which had been identified.