SOME ASPECTS OF THE ANATOMY, PHYSIOLOGY AND PHARMACOLOGY OF THE UTERUS

Anatomy and Physiology of Rabbit and Rat Uteri :

The uterus in these animals is bicornuate, consisting of two horns or loops . Upward each horn or loop is attached to an " oviduct " . Although the uterine horns appear to be fused distally, there remain two distinct " ossa uteri " opening into the vagina . Each opening has its own ostium internum and externum, as well as cervical canal (Figures 1 and 2) . The pregnant uterus is thicker than the non - pregnant and contains one or more embryonic sacs which contain the embryo (s) (Baker et al., 1979 ; Kaplan and Timmons, 1979) .

The uterine muscle consists of " visceral smooth muscle " fibres which are arranged in sheets or bundles and the cell membranes contact each other at multiple points to form many " gap junctions " or " nexi " .

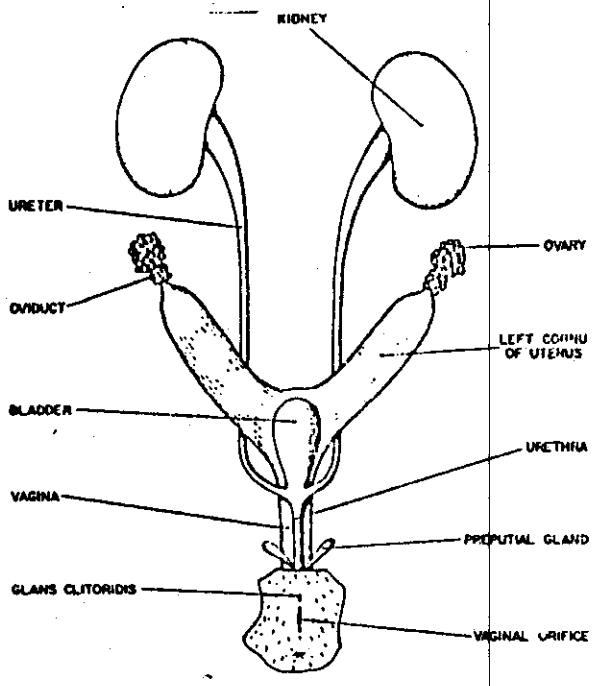

Fig. (1): Female urogenital system.

(After Baker et al., 1979) .

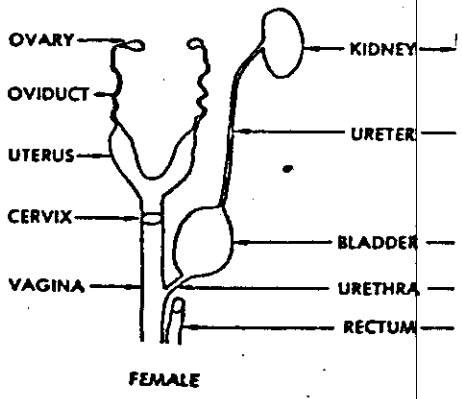

Fig.(2): Urogenital organs of female rabbit .

(After Kaplan and Timmons, 1979) .

Thus, the fibres form a functional syncytium that usually contracts in large areas at once . This type of smooth muscle is known as " single unit " or " unitary smooth muscle " (Guyton, 1982 ; Ganong,1983). When a part of a visceral smooth muscle tissue is stimulated, the action potential is conducted to the surrounding fibres by " ephatic conduction " . This means that the action potential generated in one area of the muscle electrically excites the adjacent fibres. Visceral smooth muscle fibres can transmit action potential one to another in this manner because the " gap junctions " between adjacent fibres exhibit greatly enhanced permeability so that the electrical resistance between the inside of one fibre and the next is only a fraction of the normal membrane resistance . This allows easy flow of current from the interior of one cell to the next and therefore, allows ease of transmission of action potentials over the surface membrane of the muscle mass (Guyton, 1982) .

Uterine smooth muscle is characterized by instability of its membrane potential and by the fact that

it shows continuous irregular contractions that are independent of its nerve supply . This maintained state of partial contraction is called tonus or tone and because of this continuous activity, it is difficult to study the relation between the electrical and mechanical events in visceral smooth muscle (Wilson, 1979) .

The excitation contraction coupling in visceral smooth muscle is a very slow process compared to skeletal or cardiac muscle . Calcium is involved in initiation of contraction of smooth muscle (Huxely , 1979) . The final event in initiating a myometrial contraction, is the release of Ca^{++} from its repository form in sarcoplasmic reticulum . The consequence of this event is to elevate the concentration of intracellular free calcium which may then become associated with the myofibrils of the uterine muscle . This interaction will give rise to uterine contraction , whereas the ATP energy dependent translocation of Ca^{++} back to a stored form is associated with uterine relaxation (Ganong , 1983) .

Autonomic Innervation and Types of Receptors in Uterus :

The uterus is innervated by sympathetic and parasympathetic nerve supply (Pritchard and Mac Donald , 1980) . The uterus contains cholinergic receptors where the transmitter is acetyl choline and adrenergic receptors (alpha and beta adrenoceptors) where the transmitter is noradrenaline (Wilson , 1979 ; Krall et al., 1981) . The alpha activity is excitatory while the $beta_2$ activity is inhibitory (Crossland , 1980) .

The effect of adrenergic stimuli on the uterus is variable depending on animal species, stage of sex cycle, amount of circulating oestrogen and progesterone, pregnancy and other factors (Thorbert et al., 1979) . Smooth muscle in general, including the uterus, is stimulated by acetyl choline . The effect of acetyl choline is not blocked by ganglion blocking agents . Acetyl choline seems to act on the smooth muscle membrane (Ganong , 1983) .

Effect of Pregnancy on Uterine Activity :

During pregnancy, there is high level of oestrogen and progesterone which affect markedly the uterine activity (Yen and Jaffe, 1978) . Asynchrony of the electrical and mechanical activity in rat and rabbit myometrium was reported at advanced pregnancy (Scapo, 1961) .

Effect of Oestrogen on Uterine Activity :

Oestrogen increases the amount of muscle and its contents of contractile proteins . It stimulates the synthesis of actomyosin and production of high energy organo-phosphates (Scapo, 1961) . Under the influence of oestrogen, the uterine muscle becomes more active and excitable and action potential in individual muscle fibres becomes more frequent as it decreases the membrane potential (Wilson, 1979) .

The oestrogen dominant uterus is also more sensitive to oxytocin (Fity Patrick, 1961) . There is evidence that oestrogen influences the excitability

of uterine muscle by changing the binding of Ca^{++} in the muscle . Oestrogen also affects the uterine activity in non - pregnant uterus as uterine smooth muscle is relatively inexcitable during dioestrus and in ovariectomized animals (Berger and Marshall, 1961 ; Ganong , 1983) . During oestrous phase or in oestrogen-treated ovariectomized animal, excitability and tonus is enhanced . Spontaneous contractions occur as well as, there is an increase in the sensitivity to stimuli (Fity Patrick, 1961) .

Effect of Progesterone on Uterine Activity :

Progesterone inhibits the electrical and contractile activity of the uterus . It increases the membrane potential , thus diminishes the excitability of the muscle (Wilson, 1979) . Progesterone has no significant effect on contractile elements of smooth muscle as does oestrogen (Saldivar and Melton, 1966) .

Kao and Nishiyama (1964) showed that parentral progesterone in ovariectomized rats and rabbits had no effect on the electrical and mechanical activity of

the myometrium, while Saldivar and Melton (1966) studied these effects " in vivo " and " in vitro " on the rat myometrium and reported that progesterone inhibited the rat uterus .

The experiments done by Kumar et al., (1962) proved that progesterone inhibited human myometrium " in vitro " . Moreover , Scapo (1963) demonstrated this inhibition on the rabbit uterus .

Effect of Catecholamines on Uterine Activity :

This effect is variable depending on the stage of oestrous cycle, the amount of circulating oestrogen and progesterone, pregnancy, species and other factors (Wilson, 1979) . Adrenaline relaxes the pregnant human uterus (Thorbert et al., 1979 ; Crossland , 1980), contracts the rabbit uterus (Crossland, 1980 ; Frederick and Ashton, 1982) and relaxes the uterus of the rat and non - pregnant cat (Crossland, 1980 ; Krall et al., 1981) . The nature and site of action of adrenaline on smooth muscle are not known (Daniel, 1967) .

Noradrenaline has similar action on smooth muscle but high concentrations are needed to elicit a similar response (Meyer et al., 1980) .

Effect of Prostaglandins on Uterine Activity :

Prostaglandins E and F (PGE & PGF) will initiate or augment uterine contractions throughout pregnancy not only at term (Meyer et al., 1980) .

$PGF_{2\alpha}$ stimulates the myometrium during mid - trimester and term both " in vivo " and " in vitro " . The myometrial sensitivity to PGs is higher at term than during the mid - trimester and it has been used successfully not only for induction of labour but also for induction of abortion (Bearyley and Dewhurst, 1970 ; Karim and Filshie , 1970) .

Many workers demonstrated the release of PGs from uteri of several species at term and late pregnancy (Tothill et al., 1971; Vane and Williams , 1973) . It was reported that epinephrine reversal on the rat uterus was due to liberation of PGE_2 which was only

released during oestrous cycle and late pregnancy but not in dioestrus (Tothill et al., 1971) . Moreover, Legros et al., (1974) showed release of PGF_2 from late pregnant rat uterus while Horton et al., (1971) demonstrated this in guinea pigs .

Adamson et al., (1967) observed tachyphylaxis of the rat uterus to PGE_1 . On the contrary, Paton and Daniel (1967) found the opposite .

Anderson (1981) found that indomethacin inhibited the effect of prostaglandins on uterine activity .

It was reported that strips of uterine myometrium " in vitro " relax when they are exposed to prostaglandins E (particularly E_1), but contract in response to F prostaglandins (Crossland , 1980) . However , Horrobin et al., (1978) demonstrated that PGE_2 , thromboxane and prostacycline were found to cause either contraction or relaxation .