GENERAL DISCUSSION
GENERAL DISCUSSION

The endocrine and reproductive functions of the gonads are maintained and regulated by the actions of follicle-stimulating hormone and lutenizing hormone. In higher vertebrates, FSH and LH exert characteristic effects upon specific target cells in the testis and ovary. The actions of LH are predominantly directed for steriodogenesis and ovulation, while FSH acts upon germ cells causing their development and maturation. It is now well recognized that many, if not all, of the effects of gonadotropic hormones are mediated by cAMP. LH and FSH have been shown to increase cAMP levels in the Graafian follicles (Tsafiriri et al., 1972a), granulosa cells (Kolena and Channing, 1972) and corpora lutea (Marsh et al., 1966) of the ovary and in the Leydig cells and Sertoli cells (Means et al., 1974; Dorrington et al., 1974b) of the testis.

Besides gonadotropic hormones, prostaglandins and catecholamines also appear to be involved in ovarian function. Exogenous prostaglandins mimic most of the biological and biochemical responses of LH in ovary in vivo and in vitro (Speroff and Ramwell, 1970; Marsh, 1971; Osterman and Hammond, 1978). The present study shows that prostaglandins and catecholamines play an important role in the modulation of ODC in the testis. Kuehl et al. (1970b)
advanced the hypothesis that PGE is interposed between LH and cAMP in the regulation of steroidogenesis and thereby functions as a second messenger instead of cAMP. However, various other experimental data argue against this theory. The stimulatory action of LH on cAMP is a rapid one (few minutes), while the effect of LH on PGE production was observed only after 2-5h (LeMaire et al., 1973; Marsh et al., 1974; Bauminger and Lindner, 1975). The precise position of PGE in the regulation of steroidogenesis still remains to be established. In the present study prostaglandins were found to cause stimulation of cAMP and OX activity in the testis. Stimulation of cAMP was observed at 30 min after the injection of the prostaglandins while ODC levels were found to increase at a much later time of 2h. In addition to this, MIX a phosphodiesterase inhibitor, caused an additive effect with PGE$_2$. These observations indicate that the action of prostaglandins may be mediated by cAMP in the testis of rat.

Catecholamines also appear to play an important role in ovarian function. Both rat and rabbit corpus luteum have been found to contain a gonadotropin responsive adenyl cyclase system that is also responsive to $\beta$-adrenergic catecholamines (Birnbaumer et al., 1976). They have observed that stimulatory effects of LH and catecholamine were not additive; hence they concluded that the same adenyl
cyclase system is responsive to both of these agents. In our study stimulation of ODC by catecholamines appears to be mediated through a mechanism involving α-adrenergic receptors. Furthermore, since α-adrenergic blocking agents inhibit FSH and LH induced ODC activity, catecholamines appear to be involved in the mediation of these gonadotropic hormones in the testis.

Another feature of the present investigation is the regulation of testicular function by luteinizing hormone releasing hormone. In the recent years it has been observed that LHRH and its agonists act directly on the testis. Most of the direct effects of LHRH observed in the testis and in ovary appear to be inhibitory. However, the effect of LHRH and its analogs on granulosa cell vary from inhibitory to stimulatory depending upon the experimental conditions used and parameters examined. In the present study, LHRH was found to increase testicular ODC levels in the Leydig cell fraction. The mechanism of action of LHRH in causing stimulation of ODC is paradoxical. Recently the stimulatory effects of LHRH in granulosa cells were shown to be associated with increased levels of prostaglandins (Clark et al., 1980; Clark, 1982). This gives rise to the possibility that LHRH stimulation of ODC activity in the testis is probably mediated by prostaglandins. This possibility
could not be confirmed as aspirin, a prostaglandin synthetase inhibitor did not inhibit LHRH induced ODC activity. Thus the mechanism of induction of ODC by LHRH needs further elucidation.

Another notable feature of the present work is the phenomenon of desensitization of testicular ODC by gonadotropin hormones, prostaglandins, catecholamines and LHRH. During desensitization the initial loss of measurable receptors appears to be due to receptor occupancy by the hormones whereas the secondary refractory state is accompanied by real loss of receptors (Catt et al., 1979c). Studies on the kinetics of desensitization reaction indicate that down regulation of the receptors may not be the only factor involved in the decrease of hormone dependent adenyl cyclase activity (Johnson et al., 1978; Saez et al., 1979; Su et al., 1979). The other mechanisms involved may be modification of the coupling system between receptor and adenyl cyclase (Saez et al., 1978a) or blockage of some step beyond cAMP formation (Haour and Saez, 1978; Tsuruhara et al., 1977; Saez et al., 1978b). The synthesis of an endogenous protein inhibitor triggered by agonist may also be necessary for the development of the refractory state. Such an inhibitor appears to act by interfering with the coupling of the hormone-receptor complex to the catalytic subunit of adenyl cyclase (Lamprecht et al., 1979). In this study, both types
of desensitization namely homologous and heterologous, have been observed. The mechanism of desensitization in this study appears to be due to inhibition of ODC at a step before cAMP formation for epinephrine and due to a post cAMP block in the case of prostaglandins.

Polyamines are mainly associated with growing and embryonic tissue. Recent studies have indicated that the rise in ODC activity may be related to cell proliferation in various tissues in vivo (Inoue et al., 1975; Kato et al., 1976; Takigawa et al., 1977; Poso and Janne, 1976). Testis is an actively dividing organ. This study shows that DFMO causes reduction in the levels of ODC in the testis. However, reduced levels of ODC do not cause any effect on the content of DNA, RNA and protein. Fozard et al. (personal communication) have also observed that DFMO at a dose of 200mg/kg given every six hours, for 5 days did not affect the histology of the testis. Thus depletion of polyamine levels in the testis appear to cause no effect on spermatogenesis in rats.