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I. INTRODUCTION

During vertebrate oogenesis, meiosis is arrested at late prophase of the first division (i.e., duplication of the diploid number of chromosomes of the species). The duration of this arrest varies widely according to the species, between a few days in some fishes to several years in mammals. Oocytes at that stage (dictiate or germinal vesicle stage) possess a huge nucleus, the germinal vesicle (GV), containing decondensed chromosomes. Meanwhile, oocyte volume increases considerably in many species due to the accumulation of cellular organelles and metabolic reserves essential for fertilization and embryonic development.

The terms "oocyte maturation" or "meiotic maturation" indicate the resumption of the meiotic process at the end of this growth period, which gives rise to the female gamete competent for fertilization and embryonic development. In most vertebrates, maturation is first triggered before ovulation by endocrine signals under hypothalamo–hypophysial control and lasts until another arrest occurs (generally at second division metaphase). Although temporally linked, maturation and ovulation are two different processes, each regulated in specific ways (Schuetz, 1986; Hayashi *et al.*, 1987). Fusion with the fertilizing sperm triggers completion of the maturation process.

The progression of oocyte maturation is generally estimated with the help of readily observable morphological criteria, resulting mainly from nuclear changes (germinal vesicle breakdown, or GVBD), first polar body emission, or the presence of a metaphase spindle. However, the usefulness of such criteria should not conceal the fact that the concept of maturation includes a

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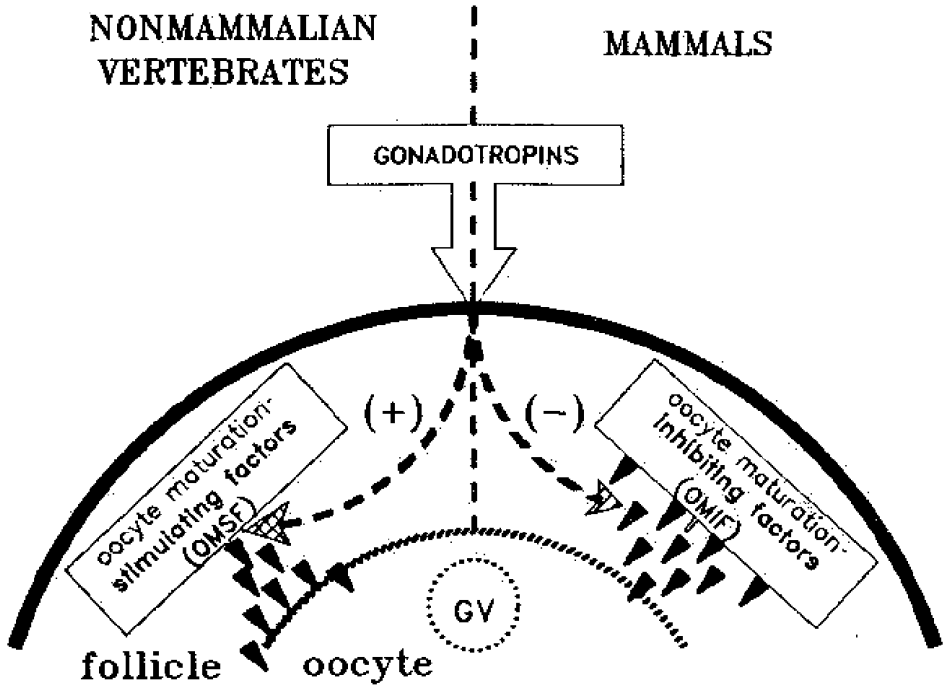

Fig. 1. Schema of the gonadotropic control of intrafollicular oocyte maturation in vertebrates. Gonadotropins would act mainly by stimulating the production of stimulating factors (OMSF) in nonmammalian vertebrates, whereas they would principally suppress the action of inhibiting factors (OMIF) in mammals.

series of complex morphological and biochemical changes at the levels of membrane and cytoplasm (and yolk in lower vertebrates), as well as nucleus, and involves the acquisition of the competence for further development (see review by Masui and Clarke, 1979).

Oogenesis is a long, complex process of cell differentiation that leads to the production of ovulated oocytes. They must be produced at the right time according to the ecophysiological requirements of each species. Adjustments between the specific endogenous rhythms of differentiation and the appropriate environmental cues are performed by the central nervous and endocrine systems. Oocyte maturation and ovulation appear as the last phase of oogenesis, which can be initiated to some extent by environmental factors. It is well known that oocyte maturation in vertebrates is under the control of the hypothalamo–hypophysial system acting through the whole follicle by means of gonadotropins. Depending on the species, gonadotropins may stimulate the production of oocyte maturation-stimulating factors (OMSF), block the production of oocyte maturation-inhibiting factors (OMIF), or both (Fig. 1). There has been so far a general agreement that pituitary gonadotropins induce oocyte maturation through the stimulation of follicular production of steroid hormones acting directly on the oocyte in amphibians and fishes (reviewed by Masui and Clarke, 1979) and through inhibition of the follicular production of OMIF in mammals (reviewed by Tsafriri, 1985; Thibault *et al.*, 1987). Arguments will be presented here to show that such a dichotomy should be considered as excessively simplistic. For example, an activity attributed to a

"meiosis-inducing substance," because it is able to induce meiosis in fetal mouse testis *in vitro*, was also detected in preovulatory human and bovine follicular fluid after the luteinizing hormone (LH) surge (Westergaard *et al.*, 1984, 1985). This substance, probably lipidic or of steroidlike nature, was therefore hypothesized to be also an important inducing factor for the resumption of female meiosis. Furthermore, pituitary gonadotropins could generate within mammalian cumulus cells a positive signal able to stimulate GVBD in the continuous presence of inhibitory factors (Downs *et al.*, 1988). Moreover, we will discuss experimental evidence showing that the follicle produces various kinds of mediators not only acting at the oocyte level but also regulating hypothalamo–hypophysial activity and even its own activity. From a general point of view, oocyte maturation is a critical step of oogenesis, which must be thoroughly regulated at different levels: the oocyte itself, the somatic ovarian tissues, and the hypothalamo–hypophysial system. Oocyte maturation and ovulation normally result from a harmonious cooperation between these different levels due to the interplay of various kinds of regulators.

The aim of this chapter is to present a comparative assessment of our present knowledge of the cellular and endocrine mechanisms that cooperate to control oocyte maturation in various vertebrate classes. We have essentially limited ourselves to *Osteichtyes* (mainly teleosts), amphibians, birds, and mammals in which the available data are consistent enough to permit the elaboration of tentative partial models exhibiting complementary features.

II. OVARIAN CONTROL OF OOCYTE MATURATION

The numerous studies on ovarian and follicular structure in vertebrates will not be reviewed in detail, and the data presented will rely on morphological evidence reviewed elsewhere (Harrison and Weir, 1977; Dodd, 1977, 1986; Thibault and Levasseur, 1979; Guraya, 1986). Only general features will be given, in particular those in which the methods used are of interest.

In all vertebrates, each oocyte is enclosed in the ovary within a single anatomical structure, the follicle, which behaves to some extent as an independent physiological unit. There are, however, important differences in the follicular structure of mammalian and nonmammalian vertebrates (Fig. 2).

In nonmammalian vertebrates, the preovulatory oocyte is generally a huge cell (from less than 1 mm to several centimeters in diameter, depending on the species), with a large amount of yolk and a large GV, more often peripherally located. It is surrounded successively by an extracellular envelope, the zona radiata (future egg chorion), and by several coats of somatic cells that differ structurally and functionally: the granulosa, the internal theca, and finally the external theca in contact with the ovarian stroma. Depending on the group of

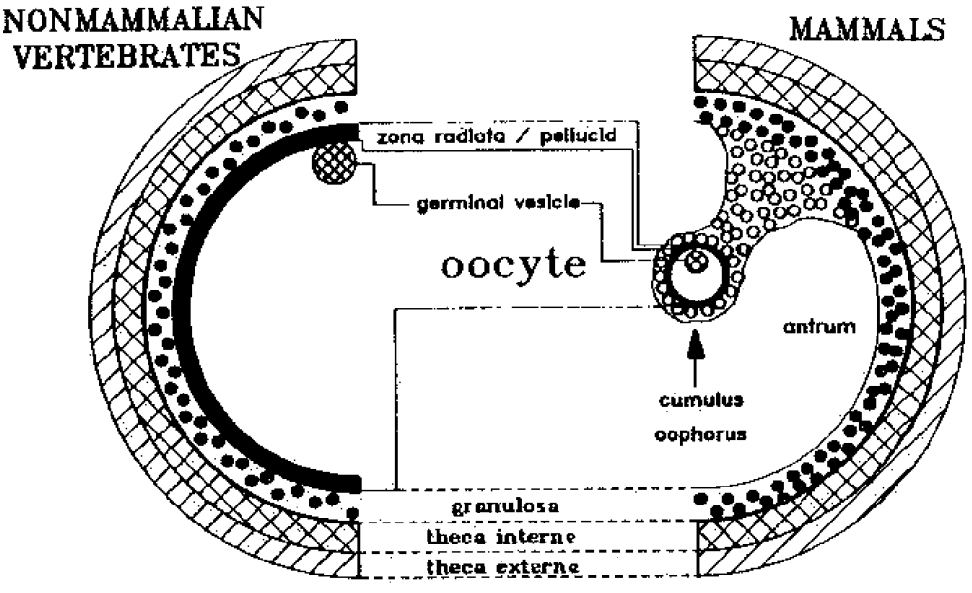

Fig. 2. Comparative schema of the morphological structure of ovarian follicle in mammalian and nomammalian vertebrates.

species, each coat of cells may be mono- or multilayered. Though apparently separated physically one from the other by the zona radiata, both the oocyte and the granulosa cell surfaces possess dense microvilli, which intermingle through the numerous radial pores in the zona radiata. In fish, a special granulosa cell located at the animal pole, the "micropylar cell," inserts a large cytoplasmic process through the zona radiata into the oocyte cortex. At ovulation, the cast of this cell becomes the micropyle, entrance of the fertilizing sperm (Yasuzumi *et al.*, 1983). The theca interna, separated from the granulosa layer by an extracellular basal lamina, is richly vascularized, whereas the theca externa includes a dense network of collagen fibers.

The mammalian oocyte is relatively small (diameter between 60 and 120 μm) and devoid of true yolk, but the preovulatory follicle may reach 0.5 to 2.5 cm in diameter. The other main difference with nonmammalian vertebrates lies in the organization of somatic cells between the oocyte and the basal lamina on the internal side of the theca interna, including the presence of an antrum (a large cavity filled with follicular fluid). Typical granulosa cells form several layers covering the internal side of the basal lamina. The oocyte is surrounded by particular granulosa cells, the cumulus cells, thus forming a morphological unity named "cumulus oophorus" or "oocyte–cumulus complex" (OCC), which projects more or less into the antral cavity through a bridge of cumulus cells. The OCC is situated either at the side of the follicle and close to the granulosa layer in species with large follicles (cattle, primates), or it keeps to the follicular center, connected to the granulosa layer by cumulus cell bridges (rodents: Thibault and Levasseur, 1979). The extracellular envelope of mammalian oocytes, the pellucid envelope, is thinner than the

zona radiata of lower vertebrates. At ovulation, some cumulus cells remain fixed to the pellucid, included within a late glycoproteic secretion, thus forming the "corona radiata," surrounding the secondary oocyte.

In order to understand how each follicular compartment can participate in the control of oocyte maturation, various kinds of experimental approaches have been performed *in vivo* and *in vitro*. The interpretation of data from *in vitro* experiments is very much dependent on the precise nature of the follicular compartments involved (see example in Fig. 3). Unfortunately, this is not always clearly specified or an inadequate terminology may be used, leading to somewhat ambiguous or even contradictory reports. Therefore we list below the usual terminology relating to experimental situations most commonly used for studying oocyte maturation:

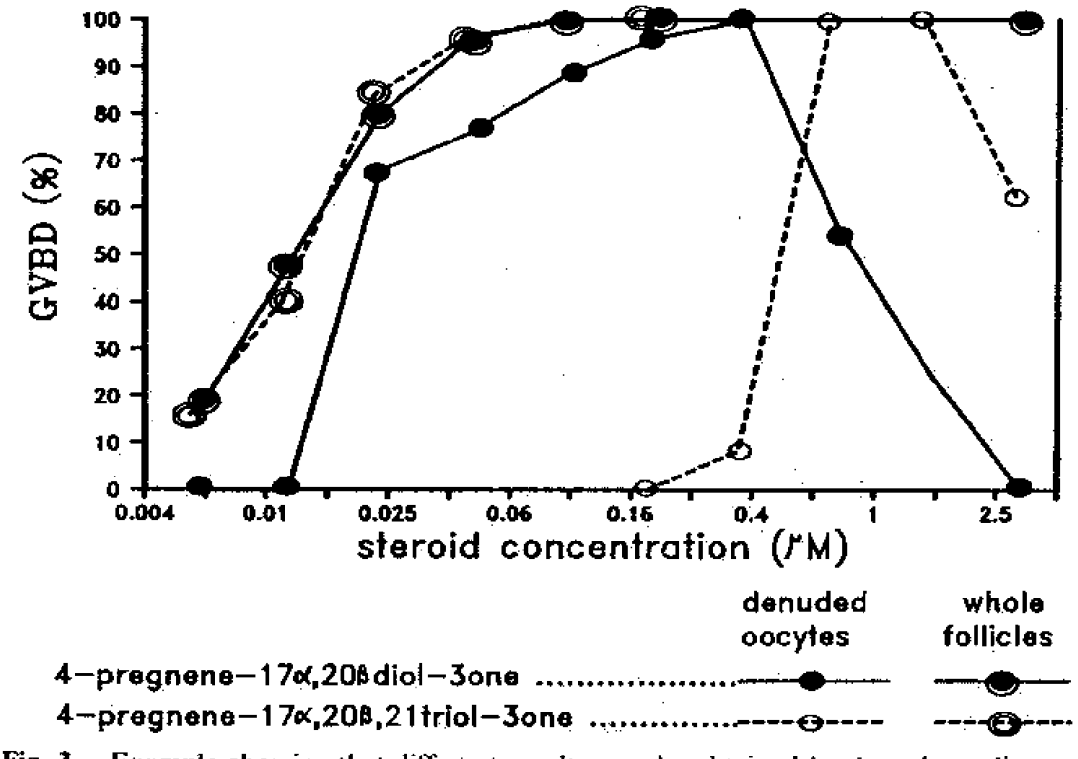

Fig. 3. Example showing that different results may be obtained *in vitro*, depending on the presence of follicular compartments. Groups of either whole follicles or of denuded oocytes from the rainbow trout *Salmo gairdneri* were cultured in various concentrations of the salmonid maturation-inducing steroid (MIS), (4-pregnene-17α,20βdiol-3one, or 17α,20β-OH-P) or of a derivative exhibiting a small structural difference, 4-pregnene-17α,20β,21triol-3one. The effectiveness of both compounds on GVBD promotion appeared identical when oocytes were cultured within their follicle, whereas the greater effectiveness of the specific MIS, 17α,20β-OH-P, was only found on denuded oocytes. Moreover, an inhibitory effect of high concentrations could be observed, for both steroids, only on denuded oocytes. Denuded oocytes were prepared by enzymatical denudation according to Finet *et al.* (1988); other technical conditions were similar to those described by Jalabert and Fostier (1984a,b).

1. *Whole perfused ovaries:* mainly in small mammals (rodents) and birds
2. *Cultured ovarian fragments* (including some ovarian stroma with groups of follicles of different size): mainly in fish and amphibians
3. *Whole follicles* (more or less devoid of surrounding ovarian stroma): all vertebrates
4. *Cumulus oophorus or oocyte–cumulus complex (OCC):* This unit, specific to mammals, may be contaminated by cells from the mural granulosa in most species except in the rabbit, where the cumulus is topographically distinct from the granulosa cell layer (Thibault *et al.*, 1987).
5. *Oocytes surrounded only by a granulosa cell layer* (usually obtained by manual dissection): commonly used in amphibians and sometimes in fish
6. *Denuded oocytes* (cleared of any follicular cells by either mechanical or enzyme treatment): ease of preparation depends on the species
7. *Naked oocytes* (devoid of pellucid membrane or zona radiata): can be prepared for special purposes (e.g., cell fusion experiments, studies on membrane receptors)

In mammals, the follicular architecture is characterized by direct cell contacts through gap junctions, allowing some metabolic exchange (between granulosa and cumulus cells and between cumulus cells and the oocyte) and by an extracellular matrix containing various glycosaminoglycans, which may also be present in the follicular fluid of the antral cavity (see Sato and Koide, 1987a, for review). Therefore, depending on the nature of putative OMIFs, their inhibitory action may either be exerted through the follicular fluid and/or the intercellular space or require direct cellular contacts between the granulosa and the cumulus cells and/or between the cumulus cells and the oocyte. The maturing gonadotropin stimulus induces a rapid evolution of the follicular architecture, or cumulus expansion, mainly due to the disruption of cumulus-to-cumulus cell gap junctions (Gilula *et al.*, 1978; Wert and Larsen, 1989) and to the secretion of glycosaminoglycans (mucification) by the cumulus cells (Dekel *et al.*, 1979). These changes are believed to play a role, which may depend on the species, in regulating the permeability of the oocyte–cumulus complex to OMIFs (Tsafriri, 1985; Sato and Koide, 1987a; Wert and Larsen, 1989).

A. Role of "Oocyte Maturation-Stimulating Factors"

Since the first work by Pincus and Enzman (1935) in the rabbit, it has been well established in mammals that morphological events of maturation, such as GVBD and metaphase spindle formation, generally occur spontaneously in oocytes removed from their follicular environment and incubated *in vitro* and can be observed easily (see reviews by Thibault, 1977; Tsafriri, 1985). However, morphological criteria are not sufficient to characterize all aspects

of complete maturation, which cannot be achieved, for most species, in oocytes deprived of any interaction with somatic cells (Thibault *et al.*, 1975a; Moor and Trounson, 1977; Thibault and Gérard, 1987; Mattioli *et al.*, 1988a). Such a discordance between morphological and functional evolution of oocytes isolated *in vitro* complicates the search for any activity actually controlling complete maturation, because research cannot rely solely on morphological observations.

Things appear clearer in lower vertebrates where follicular steroids are generally necessary to induce morphological events of maturation *in vitro*, but, in addition to the action of maturation-inducing steroids, other kinds of interactions with follicular cells might be necessary for further normal development (Iwamatsu and Ohta, 1981).

1. Steroids

No direct, clear-cut effect of steroids has been shown based on morphological criteria in mammalian oocytes cultured *in vitro*, although a high concentration of progesterone was found to accelerate maturation in the rabbit (Bae and Foote, 1975). However, when criteria such as fertilizability, that is, sperm penetration and chromosomes decondensation (human: Soupart, 1974; Botero-Ruiz *et al.*, 1984; rabbit: Thibault *et al.*, 1975b; cow: Fukushima and Fukui, 1985; pig: Mattioli *et al.*, 1988b; cat: Xu *et al.*, 1988), or developmental ability (ewe: Moor and Trounson, 1977; Moor, 1978) are considered, the importance of the steroid environment of oocytes during maturation becomes apparent. Further indirect evidence is provided by the effects of various inhibitors of steroidogenesis in gonadotropin-stimulated follicles on the maturation of enclosed oocytes. Whereas morphological maturation was not inhibited in the rat (Lieberman *et al.*, 1976; Billig *et al.*, 1983) or rabbit (Testart *et al.*, 1983) or only partially in the sow (Szölösi and Gerard, 1983) and the ewe (Osborn *et al.*, 1986), such treatments induced fertilization abnormalities in the rabbit (Yoshimura *et al.*, 1986) and in the ewe (Moor *et al.*, 1980) that were associated with abnormal patterns of protein synthesis by the maturing oocyte (Moor, 1978; Osborn and Moor, 1983a, in the ewe). Moreover, normal fertilizability of mature oocytes recovered from perfused rabbit ovaries treated with cyanoketone (inhibitor of 3β-hydroxysteroid dehydrogenase) was restored by estradiol replacement (Yoshimura *et al.*, 1987). Finally, the administration of progesterone antibodies to immature rats lowered the proportion of maturing oocytes in response to human chorionic gonadotropin (hCG) injection (Mori *et al.*, 1983), whereas the replacement of progesterone partly reverses the reduced incidence of meiosis. All the above observations suggest that steroids play a role in the control of the biochemical events of oocyte maturation in mammals (Osborn *et al.*, 1986).

In birds, the available evidence was obtained almost exclusively from observations *in vivo* in domestic birds and do not refer specifically to oocyte

maturation but to ovulation. A progesterone peak in the blood is associated with the gonadotropin ovulatory surge (hen: Shodono *et al.*, 1975; turkey hen: Mashaly *et al.*, 1976; duck: Tanabe *et al.*, 1980), and a corticosterone peak precedes (hen: Etches, 1979) or coincides with (hen: Johnson and Van Tienhoven, 1981) ovulation. The plasma ovulatory surge of LH and ovulation are blocked by administration of aminoglúthetimide, a steroid-synthesis inhibitor, and restored by injection of progesterone (Johnson and Van Tienhoven, 1984) or testosterone (Lang *et al.*, 1984) but not by estradiol, showing only an indirect role of progesterone and testosterone at the pituitary level (see Section V). Only corticosterone was able to induce ovulation without promoting a surge of LH, suggesting a direct effect on the ovary (hen: Lang *et al.*, 1984). However, *in vitro* a high concentration of progesterone induced ovulation in the fowl ovary (Tanaka *et al.*, 1987). In the latter experiment, ovaries had been isolated 16 to 18 hr before the expected ovulation time, thus prior to the endogenous preovulatory surge (Shodono *et al.*, 1975) and before the initiation of oocyte maturation (Olsen and Fraps, 1950). It may be inferred, therefore, that progesterone probably promoted both oocyte maturation *in vitro* (Wright, 1971; Snyder and Schuetz, 1973; Thibierolites could be involved in the physiological control of maturation: 17α-hydroxy,20β-dihydroprogesterone, which has been characterized as a maturation-inducing steroid (MIS; see below) in some fish, has been partially identified as a metabolite of progesterone in theca cells of the domestic hen (Marrone *et al.*, 1985).

In amphibians, cyanoketone inhibits intrafollicular, gonadotropin-induced oocyte maturation *in vitro* (Wright, 1971; Synder and Schuetz, 1973; Thibier-Fouchet *et al.*, 1976). Progesterone induces GVBD in oocytes incubated *in vitro* either within their follicle (Masui, 1967; Schuetz, 1967; Alonso-Bedate *et al.*, 1971) or after defolliculation (Smith *et al.*, 1968; Ozon *et al.*, 1975; Thibier-Fouchet *et al.*, 1976) or even devoid of zona radiata (Hirai *et al.*, 1983). Progesterone can be synthesized from its precursor pregnenolone by preovulatory follicles (Thibier-Fouchet *et al.*, 1976; Snyder and Schuetz, 1973). Progesterone plasma levels increase during the spawning season (Pierantoni *et al.*, 1987), and a peak occurs concomitently with the LH surge induced *in vivo* by GnRH gonadotropin-releasing hormone administration (McCreery and Licht, 1983). Progesterone is also produced *in vitro* by gonadotropin-stimulated ovarian pieces (Fortune *et al.*, 1975; Fortune, 1983; Hubbard and Licht, 1986; El-Zein *et al.*, 1988) and more especially by isolated follicles (Lessman and Schuetz, 1982; Schuetz and Glad, 1985). Finally, progesterone-specific bindings have been identified in plasma membrane fractions, suggesting a membrane receptor mechanism for progesterone action (Kostellow *et al.*, 1982; Sadler and Maller, 1982; Sadler *et al.*, 1985; Blondeau and Baulieu, 1984). Steroids other than progesterone, however, can also trigger GVBD *in vitro*. These can be either progesterone derivatives (Reynhout and Smith, 1973; Ozon *et al.*, 1975; Morrill and Bloch, 1977), some

of which are produced by the oocyte itself (Reynhout and Smith, 1973; Thibier-Fouchet *et al.*, 1976), or corticosteroids (Subtelny *et al.*, 1968; Schorderet-Slatkine, 1972; Jacobelli *et al.*, 1974; Morrill and Bloch, 1977; Ishikawa, *et al.*, 1977) and androgens such as testosterone (Smith and Ecker, 1971; Morrill and Bloch, 1977; Le Goascogne *et al.*, 1985). The latter are produced under gonadotropic stimulation by the preovulatory follicle (Fortune and Tsang, 1981; Hubbard and Licht, 1986). Finally, it was recently observed that 17α-hydroxy,20β-dihydroprogesterone, and to a lesser extent 17α-hydroxy,20α-dihydroprogesterone, are effective GVBD inducers in defolliculated oocytes from *Xenopus laevis* (Deshpande and Koide, 1985) and intrafollicular oocytes from *Rana pipiens* (Lin *et al.*, 1987). The 20α isomer was produced from 17α-hydroxyprogesterone by the oocyte itself (Thibier-Foucher *et al.*, 1976). This is interesting, from a phylogenetic point of view, when compared to the present state of knowledge in fish.

In almost all teleost species investigated, 17α-hydroxy,20β-dihydroprogesterone (17α,20β-OH-P) appears to be the most effective maturation-inducing steroid (MIS). First identified in the blood of postspawning females of the Pacific salmon, *Oncorhynchus nerka* (Idler *et al.*, 1960), its maturation-inducing potency was only demonstrated much later for different species *in vitro* (rainbow trout: Fostier *et al.*, 1973; Jalabert, 1975; goldfish and northern pike: Jalabert, 1976) and *in vivo* (*Salmo:* Jalabert *et al.*, 1976, 1980a; Bry, 1981; common carp, *Cyprinus carpio:* Jalabert *et al.*, 1977; northern pike: De Montalembert *et al.*, 1978). Since then, the *in vitro* maturation-inducing potency was confirmed in other species (see reviews by Goetz, 1983; Sundararaj *et al.*, 1985; Nagahama, 1987a; and recent works by Lutes, 1985; Habibi and Lessman, 1985; Pankhurst, 1985; Goetz and Cetta, 1985; Upadhyaya and Haider, 1986; Greeley *et al.*, 1986; Hirose *et al.*, 1987; Lin *et al.*, 1987; Canario and Scott, 1987; Scott and Canario, 1987; Adachi *et al.*, 1988; Kobayashi *et al.*, 1988; Begovac and Wallace, 1988; Trant and Thomas, 1988; Haider and Moses Imbaraj, 1989). It was rigorously identified in the blood of maturing female rainbow trout (Campbell *et al.*, 1980; Diederik and Lambert, 1982) and African catfish, *Clarias gariepinus* (Dam *et al.*, 1989). In some species belonging to the suborder *Salmonoidei*, 17α,20β-OH-P can be synthesized *in vitro* by ovarian follicles (Suzuki *et al.*, 1981a,b; Sangalang and Freeman, 1988) and secreted into the culture medium in response to the highly purified maturational salmon gonadotropin s-GTH (Fostier *et al.*, 1981a; Suzuki *et al.*, 1988b) or partially purified gonadotropin (Young *et al.*, 1983a; Zhao and Wright, 1985; Van Der Kraak and Donaldson, 1986; Wright and Zhao, 1988). Chemical identification in the culture medium after gonadotropin stimulation was performed by Nagahama and Adachi (1985). Finally, binding activity for 17α,20β-OH-P and R5020 has been found in brook trout oocyte cytosol (Maneckjee *et al.*, 1989), but dissociation kinetics, affinity, and specificity do not fit well the usual features of receptors, and the binding activity decreases before maturation. Although less extensive, similar

data were recently obtained in species belonging to other orders (*C. carpio:* Kime *et al.*, 1987; *Carassius auratus:* Nagahama *et al.*, 1986; *Fundulus:* Lin *et al.*, 1987; Petrino *et al.*, 1989; *Clarias:* Suzuki *et al.*, 1987; Schoonen *et al.*, 1989; *Oryzias latipes:* Sakai *et al.*, 1987). *In vivo*, a plasma surge of 17α,20β-OH-P occurs during natural maturation in trout (Fostier *et al.*, 1981b) and other *Salmonoidei* (reviewed by Goetz *et al.*, 1987) as well as in families belonging to other orders (*Cyprinidae:* Kagawa *et al.*, 1983; Shimizu *et al.*, 1985; Yaron and Levavi-Zermonsky, 1986; Santos *et al.*, 1986; *Catostomidae:* Scott *et al.*, 1984; *Hiodontidae:* Pankhurst *et al.*, 1986; *Pleuronectidae:* Hirose *et al.*, 1987; Canario and Scott, 1990; *Sparidae:* Ouchi *et al.*, 1988; *Oryziidae:* Sakai *et al.*, 1988). In trout, the plasma surge of 17α,20β-OH-P is most dominant, in comparison with other 20β-hydroxylated pregnenes and pregnanes (Canario *et al.*, 1989). In the Atlantic salmon, not only the ovaries but also the head kidneys can synthesize 17α,20β-OH-P (Sangalang and Freeman, 1988). However, 17α,20β-OH-P might not be the universal MIS in all fish. Cortisol was first proposed as an MIS in the Indian catfish, *Heteropneustes fossilis* (Sundararaj and Goswami, 1977; Sundararaj *et al.*, 1979). But according to more recent data in the same species (Sundararaj *et al.*, 1985) and in other catfish species (see above), 17α,20β-OH-P appears also to be the most effective MIS in several species from the order *Siluriformes*. Nevertheless, seasonal elevations of plasma cortisol level have been observed during the spawning season in females of various teleostean species (Bry, 1985, 1989), and cortisol might exert a positive synergistic effect at the follicular level to stimulate oocyte maturation (Jalabert, 1975) or be involved in the control of ovulation (Bry, 1985, 1989). Other candidates have recently been proposed, such as androgens (Pankhurst and Conroy, 1988) or the triols 3α/3β,17α,20β-trihydroxy-5α-pregnane and 17α,20β,21-trihydroxy-4-pregnen-3-one (Scott and Canario, 1987), the latter being the main ovarian steroid produced during final oocyte maturation in a perciform, the Atlantic croaker, *Micropogonias undulatus* (Trant and Thomas, 1986, 1988). Nevertheless, 17α,20β-OH-*P* predominates in rainbow trout plasma (Canario *et al.*, 1988).

In conclusion, steroids always appear to be involved in the control of complete oocyte maturation in vertebrates, although no general model can be proposed. It must be emphasized, however, that it is principally progestins that elicit stimulatory effects on GVBD in lower vertebrates. In some cases, corticosterone, deoxycorticosterone, and testosterone appear effective. Estradiol, which is the main steroid involved in follicular growth, is ineffective or inhibitory to GVBD and appears to be more involved in the acquisition of fertilizability and developmental competence in mammals.

2. *Peptides*

Studies *in vitro* suggest that peptidic factors might exert a physiological action on the control of oocyte maturation, either directly at the oocyte level

or indirectly via some follicular mediation. Among these, only growth factors have been reported to act unambiguously at the oocyte level, although action at the follicular level can also be demonstrated.

Buserelin, a gonadotropin-releasing hormone agonist, may increase oocyte maturation rate in isolated oocytes (probably surrounded by cumulus cells) from a primate, *Macaca fascicularis* (Lefèvre *et al.*, 1988). Insulin increases the rate of spontaneous maturation of isolated pig oocytes (Tsafriri and Channing, 1975a). Epidermal growth factor (EGF) appears able to remove the inhibition of maturation promoted by the anti-Müllerian hormone (AMH; see Section II, B, 1) in denuded rat oocytes *in vitro* (Ueno *et al.*, 1988). Insulin-like growth factors (IGFs) were recently identified in porcine and human follicular fluid (Ramasharma *et al.*, 1986), and high levels were found in preovulatory porcine follicles (Hammond *et al.*, 1985). The secretion of IGF in granulosa cell cultures is stimulated by FSH, LH, and estradiol (Hsu and Hammond, 1987).

In amphibians, insulin alone is able to induce GVBD in denuded oocytes (*Xenopus laevis:* El Etr *et al.*, 1979; Maller and Koontz, 1981; *R. pipiens:* Lessman and Schuetz, 1981). Insulin is less effective than progesterone (El Etr *et al.*, 1979), and its mechanism of action appears to be different (Stith and Maller, 1984; Deshpande and Kung, 1987). GVBD can also be induced by IGF-I at physiological concentrations, and it was suggested that insulin-induced maturation may proceed via nonspecific fixation of insulin to IGF-I receptors as distinct from both insulin and progesterone receptors (Maller and Koontz, 1981). Finally, insulin exhibits a potentiating effect on the maturation-inducing action of steroids (Le Goascogne *et al.*, 1984, 1985).

In fish, Lessman (1985) recently observed a positive synergy between insulin and various progestins on *in vitro* maturation of follicle-enclosed oocytes of the goldfish.

B. Role of "Oocyte Maturation-Inhibiting Factors"

In mammals, it is generally accepted that meiosis resumption follows removal of an inhibition that has been exerted by the follicular cells. This hypothesis was first suggested by Pincus and Enzman (1935) and further reinforced by numerous work in various mammalian species (see Tsafriri, 1985, for review). It accounts for meiosis resumption when the follicular inhibition is removed, either as the result of an appropriate gonadotropic stimulation of the whole follicle *in vivo* or *in vitro* (Ayalon *et al.*, 1972; Lindner *et al.*, 1974) or when oocytes (usually OCC) are artificially extracted from their follicle and cultured *in vitro*. Granulosa cells have been identified as the main source of the follicular inhibitory action (Foote and Thibault, 1969).

In lower vertebrates, oocyte maturation is triggered by the direct action of steroids secreted by the follicle in response to gonadotropins. Thus, the

involvement of inhibitory factors does not seem necessary to explain most of the experimental data. However, limited observations suggest that follicular oocyte maturation-inhibiting factors (OMIFs) might also exist. For example, defolliculation accelerates the response (GVBD) of *Xenopus* oocytes to progesterone (Mulner and Ozon, 1981) and increases the effectiveness of MIS in the fish *O. latipes* (Iwamatsu, 1980). In some cases, defolliculation by itself was reported to induce spontaneous maturation, such as in the fish *Fundulus heteroclitus* (Greeley *et al.*, 1987) and in certain amphibian species (Vilain *et al.*, 1980).

Different kinds of substances have been suggested as OMIF, mainly in mammals: peptides, nucleotides, nucleosides, purines, and steroids. Among all potential OMIFs, one or another may appear to play the main role, depending not only on the species but also on the experimental conditions. It is therefore impossible to establish a general hierarchy among these factors, all the more since they often appear to act synergistically.

1. Protein Factors

A particular OMIF, called the oocyte maturation inhibitor (OMI) (see reviews by Channing *et al.*, 1982; Eppig and Downs, 1984; Tsafriri, 1985; Sato and Koide, 1987a), present in the follicular fluid of a number of mammalian species, inhibits spontaneous nuclear maturation of oocytes isolated with surrounding cumulus cells from the same or other mammalian species (Tsafriri and Channing, 1975b; Gwatkin and Andersen, 1976; Jagiello *et al.*, 1977; Tsafriri *et al.*, 1977). This activity, which decreases during the course of follicular growth (Stone *et al.*, 1978, in the pig), can be overcome by LH (Tsafriri and Channing, 1975b). Production of OMI by granulosa cells (Tsafriri and Channing, 1975b) is apparently dependent on the level of hormones present within the follicular compartment, particularly FSH and androgen (Anderson *et al.*, 1985). Both OMI activity and its antagonization by gonadotropins appear to be mediated by cumulus cells, since the spontaneous maturation of denuded oocytes (devoid of surrounding cumulus cells) is not inhibited by OMI (Hillensjö *et al.*, 1979). Interestingly, the cumulus may also be a target for OMI with regard to morphological differentiation and progesterone secretion, both of which are inhibited in a dose-related manner (Hillensjö *et al.*, 1979). Attempted purification of OMI suggests that it is peptidic in nature, existing in follicular fluid as two or three molecular species (Channing *et al.*, 1982).

Other workers, however, were unable to find OMI activity in follicular fluid preparations (Sato and Ishibashi, 1977; Sato *et al.*, 1982; Liebfried and First, (1980), but a peptidic inhibitory factor called "granulosa cell factor" (GCF) was extracted from the surface of the granulosa cells and exhibited some common properties with OMI (reviewed in Sato and Koide, 1987a). Discrepancies among different authors on the characterization of OMI may be due to its lability and to differences in the methods of follicular fluid collection and oocyte culture, particularly regarding the integrity of the cellular architecture

of the isolated oocyte–cumulus complex. As underlined by Thibault *et al.* (1987), isolation of pure cumulus cell–oocyte complexes is easy in unstimulated follicles of the rabbit, because the cumulus is topographically distinguishable from the granulosa cell layer, but the recovery of granulosa-free cumulus complexes is more difficult in most other mammals because cumulus cells spread over the mural granulosa.

A glycoprotein factor, called anti-Müllerian hormone (AMH) because it causes the regression of Müllerian ducts in the fetal testis (reviewed by Josso and Picard, 1986), was also reported to prevent maturation of denuded rat oocytes (Takahashi *et al.*, 1986a). This factor is present in follicular fluid (cow: Vigier *et al.*, 1984; Necklaws *et al.*, 1986) and in granulosa cells (cow: Takahashi *et al.*, 1986b; ewe: Bézard *et al.*, 1987; rat: Ueno *et al.*, 1989). However, the maturation-inhibiting activity of AMH remains controversial, probably due to differences in the methods of preparation and assay, which might introduce artifacts (Ueno *et al.*, 1988; Tsafriri *et al.*, 1988).

Finally, inhibin, a glycoprotein hormone synthesized by the granulosa cells and present in the follicular fluid and known to act at the pituitary level to inhibit selectively the release of FSH, was also recently reported to inhibit spontaneous GVBD *in vitro* in both cumulus-enclosed and denuded rat oocytes (O *et al.*, 1989).

More work is obviously required to specify which of the above-mentioned substances have a true physiological role and can be considered as genuine "OMIs."

Although no comparable approach has been performed in fishes or amphibians, mammalian follicular fluid was reported to inhibit oocyte maturation in *Xenopus* (Cameron *et al.*, 1983; Pomerantz and Bilello, 1987).

2. *Cyclic AMP*

Cyclic AMP (cAMP) is an important intraoocyte regulator of maturation in all vertebrates (see Section III, B, 4). In some *in vitro* conditions, artificially elevated cAMP levels block nuclear maturation in isolated (defolliculated) oocytes or follicle-enclosed oocytes in various vertebrates mammals: reviewed by Tsafriri, 1985; Aberdam *et al.*, 1987; Kwon and Schuetz, 1986; amphibians: Bravo *et al.*, 1978; Maller *et al.*, 1979; Schorderet-Slatkine *et al.*, 1982; fish: Goetz and Hennessy, 1984; Jalabert and Finet, 1986; DeManno and Goetz, 1987; Finet *et al.*, 1988).

Since the first report of such an inhibitory effect in mammals (Cho *et al.*, 1974), cAMP was considered for some time to be the main follicular inhibitor of nuclear maturation, originating in the granulosa cells and transferring to the oocyte via gap junctions. Numerous conflicting or even paradoxical results have been obtained in different species under various experimental conditions (reviewed by Eppig and Downs, 1984; Tsafriri, 1985; Thibault *et al.*, 1987). It now appears most likely that cAMP is not normally transferred from follicle cells to the oocyte, even when gap junctions are still functional,

and that cAMP levels are regulated independently in each cell type (Schultz *et al.*, 1983a,b). This explains why, after gonadotropin action on the follicle, the oocyte becomes in fact committed to undergo GVBD at a time when cAMP level is increasing in the whole oocyte–cumulus complex, as observed *in vivo* in the mouse (Eppig and Downs, 1988).

There is no evidence of any transfer of cAMP from the follicular cells to the oocyte in amphibians and fish. In these vertebrates, the level of cAMP in the follicular cells and in the oocyte is probably also regulated independently. The maturation-inducing steroid (MIS) is produced in the follicular cells, at least partly by a cAMP-mediated gonadotropin stimulation involving a rise in cAMP, whereas the mechanism of MIS action at the oocyte level seems to involve a cAMP decrease (see Sections III, B, 4 and IV, A, 3).

3. *Purine Bases, Nucleosides, and Nucleotides*

Various compounds possessing a purine ring have been suggested as inhibitors of oocyte maturation. Cyclic AMP has already been discussed. In addition, substances such as purine bases, purine nucleosides, and purine nucleotides could also be involved in the inhibition of meiotic resumption.

Pig and mouse ovarian follicular fluids contain high concentrations of hypoxanthine (in the 2–4 m*M* range: Downs *et al.*, 1985; Eppig *et al.*, 1985), which can maintain *in vitro* both cumulus-enclosed and cumulus-free oocytes in meiotic arrest (Eppig *et al.*, 1985). Other purine derivatives may also be involved (Downs *et al.*, 1986; Downs and Eppig, 1987). The lack of a decrease in the concentration of hypoxanthine in mouse follicular fluid before gonadotropin-induced maturation (Eppig *et al.*, 1985) reinforces the hypothesis that gonadotropin must generate a positive maturation-inducing signal from the follicular cells in order to supercede or negate the presence of hypoxanthine in the follicular fluid (Eppig and Downs, 1987).

Adenosine, a nucleoside present in mouse follicular fluid (Eppig *et al.*, 1985), also appears to inhibit oocyte maturation (Downs *et al.*, 1986; Petrungaro *et al.*, 1986; Preston *et al.*, 1987), probably by acting at the oocyte plasma membrane (Salustri *et al.*, 1988).

Finally, hypoxanthine, adenosine, and nucleotides such as cAPP (cyclic adenosine-3′,5′-pyrophosphate) could act synergistically with cAMP to inhibit mouse oocyte maturation (Sato *et al.*, 1985; Sato and Koide, 1987b).

We recently found in fish that adenine (0.5 m*M*) blocked *in vitro* intrafollicular trout oocyte GVBD stimulated by the salmonid MIS, 17α,20β-OH-P (Garg and Jalabert, unpublished), as effectively as cAMP (Jalabert and Finet, 1986). Intermediate metabolites such as adenosine-5′monophosphate, adenosine, and inosine-5′monophosphate also inhibit 17α,20β-OH-P-induced GVBD, but much less effectively than cAMP or adenine. However, the physiological significance of such observations has to be confirmed.

In amphibians, mammals, and probably other vertebrates, various naturally occurring compounds that have a purine ring are able to exert a differen-

tial regulatory effect on adenylate–cyclase activity, depending on the cell type (Sahyoun *et al.*, 1976; Fain and Malbon, 1979). Therefore, taking into account the importance of cAMP levels in each follicular compartment for the control of meiotic arrest or resumption, it is tempting to suggest that such compounds are important intrafollicular regulators.

4. Steroids

Some ovarian steroids inhibit meiosis resumption under certain experimental conditions, although the actual physiological significance is still debatable.

Such inhibitory effects on the maturation of isolated mammalian oocytes were observed with progesterone (rabbit: Smith *et al.*, 1978), estradiol (pig: Racowski and McGaughey, 1982, only in the presence of bovine serum albumin (BSA); mouse: Eppig and Koide, 1978), and testosterone (mouse: Sato and Koide, 1987b), although the concentrations could be considered as nonphysiological (Eppig and Koide, 1978). This kind of effect may be reversible (Moore Smith and Tenney, 1980). Moreover, the administration of antiserum to estrone facilitates hCG stimulation of intrafollicular meiosis in rats (Mori *et al.*, 1979). Testosterone (pig: Rice and McGaughey, 1981) and progesterone (mouse: Eppig and Downs, 1984; Batten *et al.*, 1989) enhanced dibutyryl-cAMP inhibition of spontaneous maturation but had no significant effect when administered at concentrations similar to those found in the fraction of follicular fluid that enhances cAMP inhibitory action on mouse oocytes (Downs and Eppig, 1984). This inhibitory activity can be potentiated by estradiol or testosterone in the mouse (Sato and Koide, 1987b). However, in other studies, no correlation was found between the inhibitory capacity of the follicular fluid and its estradiol or testosterone concentration (pig: Van De Wiel *et al.*, 1983; human: Channing *et al.*, 1983). More recently, however, an androgen (19-norandrostenedione), identified in mare, sow, and human follicular fluid (Khalil and Walton, 1985; Dehennin *et al.*, 1984), amplified the inhibitory effect of dibutyryl-cAMP on nuclear maturation of cumulus-enclosed pig oocytes (Daniel *et al.*, 1986) at physiological concentrations (Khalil and Walton, 1985).

In amphibians, estradiol-17β was shown to antagonize GV migration prior to GVBD, probably by acting at the cytoskeleton level (Lessman, 1987). Estrogens, in particular estradiol-17β, are also able to inhibit progesterone-induced GVBD in denuded oocytes (*X. laevis:* Baulieu *et al.*, 1978; *R. pipiens:* Lin and Schuetz, 1983). Such inhibition requires continued exposure of oocytes to estradiol for several hours prior to the addition of progesterone and during the ulterior incubation period. Although the mechanism of this inhibition is unknown, the observation that estradiol enhances cholera toxin-induced cAMP accumulation in the oocyte (Thibier *et al.*, 1982) suggests membrane adenylate cyclase as a possible site of action. This direct membrane effect is also supported by various studies showing nongenomic actions of estradiol in mammalian somatic cells (Weiss and Gurpide, 1988).

III. INTRAOOCYTE CONTROL OF MATURATION

The onset of maturation is rapidly followed by a cascade of biochemical processes within the oocyte (Masui and Clarke, 1979). This makes it difficult to distinguish between the different steps in the transduction and amplification of the initial maturation signal and the cellular responses that represent completion of maturation itself and that are necessary for the acquisition of competence for fertilization and embryonic development.

A. General Occurrence of a Cytoplasmic "Maturation-Promoting Factor"

The emergence of an activity called maturation-promoting factor (MPF) in the cytoplasm of maturing oocytes appears to be a necessary amplification step common to all animals. The presence of MPF is characterized by the ability of the cytoplasm from maturing oocytes to cause maturation following injection into immature unstimulated oocytes. Such an activity was first observed in *Bufo bufo* and *B. viridis* oocytes and attributed to the nuclear sap (Dettlaff *et al.*, 1964), which was in fact contaminated with some cytoplasm. Masui and Markert (1971) demonstrated that the appearance of MPF activity in the cytoplasm of maturing oocytes of *R. pipiens* does not require the presence of the nucleus, and they showed its capacity for autocatalytic amplification by repeated serial transfers of cytoplasm. Afterward, MPF was found in other amphibians, (*X. laevis:* Schorderet-Slatkine and Drury, 1973; *Ambystoma mexicanum:* Reynhout and Smith, 1974), in a teleost fish, the sturgeon (Dettlaff, 1977), in mammals (mouse: Balakier and Czolowska, 1977), and in invertebrates (starfish: Kishimoto and Kanatani, 1976). It rapidly appeared not to be species-, order-, or class-specific, as demonstrated by various cross-injection experiments (Reynhout and Smith, 1974; Dettlaff, 1977; Kishimoto *et al.*, 1982; Sorensen *et al.*, 1985) and heterologous oocyte fusion experiments (Fulka, 1983). Another important property of MPF is the oscillatory character of its activity (Wasserman and Smith, 1978; Masui, 1982, 1985; Gerhart *et al.*, 1984; Hashimoto and Kishimoto, 1988), which plays an essential role in controlling the two successive meiotic cycles up to second metaphase. These oscillations of MPF activity are presently believed to result from changes in the balance between a putative inactivating factor (Gerhart *et al.*, 1984; Cyert and Kirschner, 1988) and an activating protein called "cyclin" (Murray, 1989). Cyclin, which was first discovered in fertilized sea urchin eggs where its abundance exhibits cyclical fluctuations from one cell cycle to the following (Evans *et al.*, 1983), can induce GVBD when microinjected into *Xenopus* oocytes (Swenson *et al.*, 1986) and was suggested to act as a subunit of the active MPF complex (Draetta *et al.*, 1989). Highly purified MPF preparations were recently obtained from oocytes of *Xenopus* (Lohka *et al.*, 1988) and starfish (Labbé *et al.*, 1988) by using a

sensitive cell-free bioassay for MPF activity based on the induction of membrane breakdown and chromosome condensation in isolated sperm or somatic nuclei *in vitro* (Lohka and Masui, 1983; Lohka and Maller, 1985; Miake-Lye and Kirschner, 1985), much more sensitive than the oocyte microinjection assay. Purified MPF appears as a 34 kDa protein kinase, identical to the histone H1 kinase known to be transiently activated during mitosis initiation (reviewed in Labbé *et al.*, 1989) and including one subunit homologous to the product of the cell cycle control gene $cdc2^+$ first identified in yeast (Arion *et al.*, 1988; Dunphy *et al.*, 1988; Gautier *et al.*, 1988; Labbé *et al.*, 1988, 1989). In fact, most MPF bioassays are representative only of metaphase promotion and not necessarily of the whole meiotic maturation process, which should normally develop after GVBD up to the second metaphase spindle. Therefore, genuine MPF should be defined only as a "metaphase-promoting factor." As such, it is capable of autoamplification in the absence of protein synthesis (Wasserman and Masui, 1975; Gerhart *et al.*, 1984; Cyert and Kirschner, 1988), although this point has been controversial in *Xenopus* (Drury and Schorderet-Slatkine, 1975) and mammals (Fulka *et al.*, 1988), probably due to technical particularities. In fact, a synthesis of protein (which is probably cyclin, according to Murray, 1989) is required before and after the first activation of MPF, particularly in relation to MPF activity oscillations that occur after the first metaphase (Hashimoto and Kishimoto, 1988). Further MPF amplification, which is associated with a burst of phosphorylation (Maller *et al.*, 1977; Wu and Gerhart, 1980; Capony *et al.*, 1986; Cyert and Kirschner, 1988), has been suggested to result from the autocatalytic activation of a preexisting precursor, through rapid changes in its phosphorylation level. This would directly or indirectly stimulate a cascade of phosphorylations and dephosphorylations promoting most of the cellular effects of maturation. One of these would be a reversible hyperphosphorylation of the laminal proteins, major structural proteins underlying the nuclear envelope, thus resulting in the nuclear lamina disassembly, leading to GVBD (Gerace and Blobel, 1980; Miake-Lye and Kirschner, 1985).

B. Mechanism of Action of Ovarian Factors (OMSFs and OMIFs)

The chain of events between the external signal and the appearance of MPF in the oocyte is not fully understood, even in amphibians in which many investigations have been carried out. Although limited, work in fish and mammals can, nevertheless, be compared to that in the amphibians, thus enriching a more general model for the regulation of oocyte maturation.

1. Apparent Posttranscriptional Character

There is a general agreement that resumption of meiosis involves only posttranscriptional events. MIS-induced GVBD is unaffected by transcription inhibitors in fish (Dettlaff and Skoblina, 1969; review by Goetz, 1983) and

amphibians (Schuetz, 1967; review by Masui and Clarke, 1979) in which the transitory RNA synthesis following the MIS action does not seem essential to GVBD (Morrill *et al.*, 1975). Even enucleation does not inhibit maturation in oocytes of *R. pipiens* (Smith and Ecker, 1969; Masui and Markert, 1971) and *X. laevis* (Schorderet-Slatkine and Drury, 1973), although the nuclear sap appears to be necessary to maintain the yield of MPF production in *Pleurodeles waltlii* (Skoblina *et al.*, 1984; Gautier, 1987). In the case of mammals, transcription inhibitors do not seem to block spontaneous maturation of isolated oocytes in the mouse (Crozet and Szöllösi, 1980), but data are more equivocal in the ewe, depending on the concentration of inhibitor, the time of application, and the presence of cumulus cells (Osborn and Moor, 1983b). Even in the mouse, high concentrations of inhibitors can be effective (Bloom and Mukherjee, 1972), but this is believed to be nonspecific (Golbus and Stein, 1976).

2. *Membrane Involvement*

Much of the experimental data suggest that the induction by progesterone of amphibian oocyte maturation may involve specific action at the membrane level (Baulieu *et al.*, 1985). The maturation response of *R. pipiens* depends on the area of oocyte surface exposed to progesterone (Schuetz and Cloud, 1977). Some nonhormonal compounds or hormonal factors known to act on the cell membrane can either induce GVBD or at least enhance the action of progesterone (Baulieu *et al.*, 1978; Dascal *et al.*, 1985; see also Section II, A, 2). Steroids bound to macromolecules and that cannot enter the oocyte show that the hormonal signal is effective even when restricted to the oocyte surface (Ishikawa *et al.*, 1977; Godeau *et al.*, 1978). The report of cytosolic receptors (Kalimi *et al.*, 1979) has not been confirmed and may have been due to the use of an inappropriate buffer that dissolved membrane proteins (absence of calcium and presence of ethylenediaminetetraacetate EDTA: see Pietras and Szego, 1979). The demonstration of a specific binding of progesterone to the surface membrane, by the measurement of repartition kinetics between plasma membrane, cytoplasm, and nucleus, correlates with the physiological response (GVBD) in *R. pipiens* oocytes (Kostellow *et al.*, 1982). Routine methods for the characterization of steroid receptors are inappropriate for plasma membranes, owing to a particularly high, nonspecific binding of lipophilic steroids. Moreover, the use of a synthetic progestin (R5020) displaying photoactivated covalent binding to progestin receptors revealed a 110 kD protein (Sadler and Maller, 1982; Sadler *et al.*, 1985) or a 30 kD protein (Blondeau and Baulieu, 1984). Such discrepancies make it difficult to draw conclusions from the binding data obtained by the photoaffinity method (Blondeau and Baulieu, 1984). Several experimental arguments suggest that receptor sites are located on the internal side of the oocyte membrane. Autoradiography of *Xenopus* oocytes incubated with tritiated progesterone showed labeling "at the level of the cell membrane and the

underlying cytoplasm" (Brachet *et al.*, 1974). Progesterone failed to induce maturation when microinjected with an aqueous solution but was effective when dissolved in paraffin oil in order to avoid leakage or metabolism (Tso *et al.*, 1982). Finally, GVBD can be induced in *Xenopus* oocytes by digitoxigenin, but not by digitoxin. Both digital toxins act on the membrane. Digitoxigenin is a C_{23} steroid that can get through the membrane, whereas digitoxin, which is digitoxigenin coupled to sugar residues, cannot (Cartaud *et al.*, 1984).

Fewer data are available in fish. As mentioned above (Section I), MIS-induced GVBD does not require transcriptional events, in contrast with the usual model for the intracellular action of steroids on somatic tissues. In a recent review, Nagahama (1987b) reported unpublished results (by Nagahama and Kishimoto) showing that 17α,20β-OH-P does not induce GVBD when microinjected into goldfish oocytes; but some doubt can be raised about the preservation of MIS integrity in such experiments, as in amphibians (Tso *et al.*, 1982; Thibier-Fouchet *et al.*, 1976). Further support for oocyte membrane involvement in fish comes from the observation that asterosaponins, which interact with cholesterol molecules in the cell membrane, stimulate GVBD (Voogt and De Groot, 1983).

In mammals, indirect evidence also suggests that the oocyte plasma membrane could be involved in the regulation of meiotic resumption, as a target for adenosine inhibitory effects (Salustri *et al.*, 1988).

3. Early Events at the Membrane Level

The nature of membrane events following maturation induction has been studied essentially in amphibian oocytes, in which progesterone induces different kinds of rapid and slow modification. The repartition of intramembranous particles shows a relatively rapid response taking several minutes and a slow response over several hours (Bluemink *et al.*, 1983). A similar distinction between rapid and slow changes can also be made concerning membrane fluidity (Morrill *et al.*, 1989) and other biochemical and biophysical properties. Thus, pronounced changes in membrane permeability and electrical potential, which are only noticeable after a few hours (review by Masui and Clarke, 1979; Morrill *et al.*, 1984; Richter *et al.*, 1984), appear as one of the results of the maturation process. On the other hand, certain early biochemical events seem to participate in the transduction of the hormonal signal. In particular, inhibition of membrane adenylate cyclase has been demonstrated in whole living oocytes (Mulner *et al.*, 1979) and subsequently in membrane fractions prepared from progesterone-treated oocytes (Sadler and Maller, 1981; Finidori-Lepicard *et al.*, 1981; Jordana *et al.*, 1981; Sadler *et al.*, 1985). This inhibition would explain the early decrease of cAMP found in stimulated oocytes (Speaker and Butcher, 1977; Morrill *et al.*, 1977; review by Cicirelli and Smith, 1985). Rapid changes in the activity of other membrane enzymes also appear to be involved, such as proteases (Morrill *et al.*,

1983; Morrill and Kostellow, 1986; Picard *et al.*, 1987; Ishikawa *et al.*, 1989), alkaline phosphatase (Le Goascogne *et al.*, 1987), and methyltransferases, responsible for phospholipid transmethylation (Godeau *et al.*, 1985; Chien *et al.*, 1986). The rapid activation of membrane enzymes may be promoted by rapid changes in the rate and/or level of phosphorylation. For example, progesterone rapidly inhibits the phosphorylation of a unique Mr 48,000-membrane protein in *Xenopus* oocytes (Blondeau and Baulieu, 1985). Finally, following the action of progesterone, short-term changes in membrane permeability to Ca^{++} (O'Connor *et al.*, 1977) may lead to a transient increase of internal free Ca^{++} (review by Morrill *et al.*, 1981; Morrill and Kostellow, 1986). Various drugs interacting with Ca^{++} fluxes were found to be potent GVBD inducers (Baulieu *et al.*, 1978). Therefore, Ca^{++} was believed for a time to act as a second messenger (Moreau *et al.*, 1980). However, increasing evidence suggests that Ca^{++} redistribution, which may occur rapidly at the membrane level after progesterone action, is just one consequence of the activation of a number of membrane properties, including permeability to ions, but that a rise in free Ca^{++} per se is not a necessary step in triggering oocyte maturation (Bellé *et al.*, 1977; Robinson, 1985; Cicirelli and Smith, 1987; Cork *et al.*, 1987).

4. Cytoplasmic Control of MPF Activation

In amphibians, the important role of some cytoplasmic steps in the cascade of events that follow the primary action of MIS at the membrane level is well established (see reviews by Maller and Krebs, 1980; Maller, 1983; Ozon, 1983). These are mainly fluctuations in the cAMP level and protein phosphorylations.

According to a widely held but controversial model, oocyte membrane activation would lead to a transient decrease in the intraoocyte concentration of cAMP. This, in turn, would promote a partial inactivation of a cAMP-dependent protein-kinase that was maintaining putative initiator proteins in a phosphorylated inactive form. Activation of the initiator proteins would then, via unknown steps involving protein synthesis to some extent (inhibition by cycloheximide), induce MPF activation. Although many points remain obscure or controversial, a considerable amount of data supports the above model in amphibians. The information available in fishes and even in mammals suggests that the main intraoocyte mechanisms could be very similar in all vertebrates. The importance of oocyte cAMP in the regulation of oocyte maturation was first suggested by the induction of a rise in intraoocyte cAMP levels by various substances that also inhibit maturation, whether this was induced by MIS in lower vertebrates or by release of follicular inhibition in mammals. These substances include phosphodiesterase inhibitors such as isobutylmethylxanthine (IBMX) or theophylline in amphibians (O'Connor and Smith, 1976; Bravo *et al.*, 1978), fish (Goetz and Hennessy, 1984; Jalabert and Finet, 1986; DeManno and Goetz, 1987), and mammals (Cho *et al.*, 1974)

and adenylate cyclase stimulators such as cholera toxin or forskolin in amphibians (Schorderet-Slatkine *et al.*, 1978; Mulner *et al.*, 1979; Maller *et al.*, 1979), fish (Jalabert and Finet, 1986; DeManno and Goetz, 1987; Iwamatsu *et al.*, 1987a), and mammals (Urner *et al.*, 1983; Sato and Koide, 1984). Moreover, the induction of oocyte maturation was followed by a transient decrease in oocyte cAMP in amphibians (Speaker and Butcher, 1977; review by Cicirelli and Smith, 1985), fish (Jalabert and Finet, 1986; Finet *et al.*, 1988), and mammals (Schultz *et al.*, 1983b). Although the evidence for the presence and timing of a cAMP decrease is equivocal for certain species, regulation of the intraoocyte cAMP level seems to play an important part in the control of oocyte maturation. In amphibians, this regulation, which results primarily from MIS action at the membrane level, appears to be due mainly to an inhibition of adenylate cyclase activity (cf. Section III, B, 3). Some stimulation of cytoplasmic phosphodiesterase activity may also occur (Allende and Plaza, 1987), at least when maturation is stimulated by factors such as insulin or IGF-1 (Sadler and Maller, 1987, 1989). In the mouse oocyte, phosphodiesterase regulation is also involved in the cAMP decrease associated with the resumption of meiosis (Bornslaeger *et al.*, 1984), and the meiotic arrest may be maintained by the inhibitory effect of some follicular steroids on oocyte phosphodiesterase (Kaji *et al.*, 1987). The probable involvement of the cAMP-dependent protein-kinase (PK) in the regulation of meiosis resumption, as a corollary of cAMP decrease, was first demonstrated by microinjections of either the regulatory or the catalytic subunit of PK, which respectively stimulated or inhibited GVBD in the amphibian *Xenopus* (Maller and Krebs, 1977; Huchon *et al.*, 1981), as well as in the mouse (Bornslaeger *et al.*, 1986).

However, even though the involvement of cAMP as an important intraoocyte regulator of maturation is supported by a considerable body of evidence, as reported above, some data suggest that a decrease in oocyte cAMP would not be necessary nor sufficient to trigger maturation and that other parallel or alternative cytoplasmic signaling pathways could be involved. Thus, maturation can be induced in *Xenopus* by some agents that promote an increase instead of a decrease of cAMP, such as Mg^{++} microinjections (Bellé *et al.*, 1986) or adenosine action (Gelerstein *et al.*, 1988). Conversely, acetylcholine, an agent that lowers the intraoocyte level of cAMP, does not promote maturation by itself but accelerates progesterone-induced maturation in *Xenopus* (Gelerstein *et al.*, 1988). In the rainbow trout, *Salmo gairdneri*, 17α,20β-OH-P administered at concentrations too low to induce maturation is able to promote the same decrease in oocyte cAMP as do higher maturation-inducing concentrations (Finet *et al.*, 1988).

The possible occurrence of at least another maturation-regulating pathway has also been suggested in amphibians by the fact that GVBD can be promoted by a direct action at the oocyte membrane level, not only of maturation-inducing steroids but also of insulin or growth factors such as

IGF-I (see Section II, A, 2). The latter appear to act through different mechanisms, partially independent of cAMP (Stith and Maller, 1984, 1987; Deshpande and Kung, 1987; Sadler and Maller, 1987) but involving the Ca^{++}-dependent protein-kinase C (PKC) (Stith and Maller, 1987; Kleis-San Francisco and Schuetz, 1988). As in other cell types, PKC could be activated by diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3) produced as a result of membrane phosphoinositide hydrolysis stimulated by insulin or IGFs. In mammals, where the nature of external maturation signals is still unknown, PKC also appears as one of the intracellular signaling pathways possibly involved in the control of maturation (Lefèvre *et al.*, 1988).

IV. REGULATION OF THE OVARIAN ACTIVITY RELATED TO OOCYTE MATURATION

A. Role of Pituitary Gonadotropins

1. Nature

In mammals and most birds and tetrapod lower vertebrates, the existence of two chemically distinct types of gonadotropic hormones, LH and FSH, is well established, although their respective biological activities are sometimes not clearly distinguished, especially in amphibians and some reptiles (see Licht *et al.*, 1977, for review). According to an oversimplified scheme, FSH is involved mainly in the control of follicular growth, whereas LH is considered to control mainly ovulation-linked events, including oocyte maturation. However, either FSH or LH is effective in mammals whose oocytes can mature within cultured follicles *in vitro* in response to gonadotropins (Lindner *et al.*, 1974). FSH can be even more effective than LH in promoting maturation, whereas LH is more effective than FSH in stimulating progesterone secretion (Neal and Baker, 1975). Considering that plasma levels of both gonadotropins show a preovulatory rise (Schwartz, 1974), they may certainly act synergistically (Labhsetwar, 1970).

The actual number of gonadotropins in teleostean fishes has been controversial, particularly when the control of vitellogenesis in the female is concerned (reviewed by Idler and Ng, 1983). One gonadotropin, called "maturational GTH," which occurs generally in all teleostean species in which it has been looked for, was biologically characterized by its ability to induce intrafollicular oocyte maturation *in vitro* in rainbow trout (Jalabert *et al.*, 1974; Breton *et al.*, 1976). However, numerous studies have been using a partially purified preparation, SG-G100 (Donaldson *et al.*, 1972), obtained by chromatography on sephadex G100 of an acid acetone extract from salmon pituitaries. More recently, two gonadotropins, GTH I and GTH II, have been isolated from the pituitary of the amago salmon, *Oncorhynchus rhodurus* (Suzuki *et al.*, 1988a); both stimulate ovarian steroidogenic activity in this

salmon. GTH II, which is more effective than GTH I on the the stimulation of 17α,20β-OH-P production by postvitellogenic ovarian follicles *in vitro* (Suzuki *et al.*, 1988b), is probably equivalent to the maturational GTH already characterized. GTH I appears to be distinct, particularly concerning the amino acid sequence of its β-subunit (Itoh *et al.*, 1988). Finally, the plasma levels of each of these GTHs appear to fluctuate differently throughout the reproductive cycle, GTH I keeping at a lower level from GTH II at ovulation (Suzuki *et al.*, 1988c). Although the specific biological activities of teleost GTH are different from those commonly used to characterize LH or FSH, some similarities with mammalian gonadotropins can be found in their chemical properties (Burzawa-Gerard, 1982) and their structural characteristics, especially of the β-subunit (Jollès *et al.*, 1977; Itoh *et al.*, 1988). The acronym GTH will be used in the present review to refer to the maturational gonadotropin, equivalent to GTH II according to Suzuki *et al.* (1988a).

2. *Endocrine Signals*

In mammals, as in all vertebrate species, oocyte maturation and ovulation are preceded by an increase in the plasma levels of gonadotropins. This increase is usually termed the "ovulatory surge" because ovulation is normally the end point of processes that begin with the initiation of meiosis resumption and are triggered by gonadotropins. Thus, in the rat, an LH peak occurs simultaneously with an increase of FSH in the afternoon of proestrus, when the oocytes' ability to resume meiosis is acquired, and FSH thereafter shows a secondary rise in the morning of estrus (Ayalon *et al.*, 1972). In the hamster also, a surge of both hormones appears necessary at the time of proestrus, so that subsequent preovulatory events can occur (Sheela Rani and Moudgal, 1977a,b). The second FSH surge, in the species where it occurs, may initiate differentiation of a new set of follicles for the next cycle (Sheela Rani and Moudgal, 1977a). The respective preovulatory increases of LH and FSH do not seem to always depend on the same mechanism, however. The simultaneous preovulatory rise of both hormones during proestrus appears to be promoted by an augmentation of the amplitude and frequency of secretion pulses (Elias *et al.*, 1982; Walters and Schallenberger, 1984) as a result of GnRH pulsatile secretion (McNeilly *et al.*, 1984). In contrast, the second phase of increased plasma FSH concentration may reflect an increase in the basal FSH secretion rate (Elias and Blake, 1981 a,b).

In the hen, a biphasic LH surge occurs before ovulation (Williams and Sharp, 1978), but there is no FSH increase (Scanes *et al.*, 1977) (see Section V).

Most information on the lower vertebrates has come from teleostean fish (reviewed by Idler and Ng, 1983). In the trout, endocrinological data can be precisely related to the progress of oocyte maturation followed *in vivo* by repeated biopsies: GVBD is preceded by a rise in plasma GTH (Fostier *et al.*, 1978; Breton *et al.*, 1983), associated with a sharp increase of MIS, 17α,20β-

OH-P (Fostier *et al.*, 1981b; Fostier and Jalabert, 1986). The form of the rise in GTH differs from that of the ovulatory surges usually found in mammals. It is initiated after modification of the pulsatile pattern of the GTH secretion prevailing during the end of vitellogenesis into a circadian rhythm (Zohar *et al.*, 1986). Such a modification of the GTH secretion pattern could account in part for the shift in the ovarian steroidogenic ability observed at that time (Zohar, 1982), characterized by the inhibitory action of GTH on aromatase activity involved in estradiol synthesis (De Monès, 1987; De Monès and Fostier, 1987) and its stimulating action on MIS (17α,20β-OH-P) synthesis (Fostier *et al.*, 1981a). The scheme of endocrine signaling of oocyte maturation might exhibit major variations among various classes of fish, however, and the salmonid model should not be generalized. In cyprinids, for example, a typical ovulatory surge of GTH was observed in the goldfish (Stacey *et al.*, 1979) and in carp (Santos *et al.*, 1986).

3. Mechanism of Action

The first step of gonadotropin action in the ovary is the binding to ovarian receptors. The total number of receptors increases during the process of oocyte maturation in the amago salmon (Kanamori and Nagahama, 1988a) and in the brown trout *Salmo trutta* (Breton and Sambroni, 1989), as well as in mammals (Kammerman and Ross, 1975), leading to an enhanced follicular sensitivity to gonadotropins in terms of steroidogenic potential (Kanamori and Nagahama, 1988a; see Section VI). The regulation of LH and FSH receptors has been particularly well studied in mammalian granulosa cell cultures (reviewed by Richards, 1980). The number of FSH receptors in granulosa cells, which remains essentially constant during follicular growth, increases during metestrus and diestrus 1 and decreases during diestrus 2 and proestrus (Uilenbroek and Richards, 1979; Uilenbroek and Van der Linden, 1983) at the expected time of oocyte maturation. These receptors can be induced by FSH itself, but only in the presence of estradiol (Louvet and Vaitukaitis, 1976; Tonetta and Ireland, 1984), which might be the limiting regulator of follicular development (Farookhi, 1980). The number of LH receptors increases from diestrus to proestrus (Nimrod *et al.*, 1977) simultaneously with the follicle's ability to produce cAMP and estradiol. Even though LH appears to regulate its own receptors (Rao *et al.*, 1977), FSH is required for their induction (Zeleznik *et al.*, 1974; Richards *et al.*, 1976), as the result of a *de novo* synthesis (Segaloff and Limbird, 1983; Loeken and Channing, 1985). Moreover, the action of FSH on the induction of LH receptors is greatly stimulated by estradiol (Sheela Rani *et al.*, 1981; Knecht *et al.*, 1985a,b), which thus seems to play an important role as an autocrine ovarian regulator of gonadotropin action by its differential effect on LH and FSH receptors.

Ovarian steps following gonadotropin binding and leading to oocyte maturation should differ in mammals in which the suppression of putative matura-

tion inhibitors is considered to be the main maturation-inducing mechanism and in lower vertebrates in which the main mechanism seems to be the induction of MIS synthesis. In both cases, however, the preovulatory gonadotropic surge acts, among other possible effects, upon ovarian steroidogenesis, in particular stimulating progestin production (see Section IV, B), whether or not these, in turn, can directly trigger oocyte maturation.

There is good evidence from numerous studies that the effect of gonadotropins on steroidogenesis is mediated in part by a rise in intracellular cAMP, through the stimulation of membrane-bound adenylate cyclase (see reviews by Marsh, 1976, and Cooke, 1983). Another cyclic nucleotide, cGMP, which is known to exhibit fluctuations in response to gonadotropin stimulation, was recently suggested to play a role by activating cAMP-phosphodiesterase, thus lowering the cAMP level after its initial gonadotropin-induced rise (Hubbard and Price, 1988). Other kinds of intracellular messengers are probably involved, such as inositol-triphosphate (IP_3) and diacylglycerol (DAG), by-products of gonadotropin-stimulated phosphoinositide metabolism that are expected to act on intracellular Ca^{++} mobilization and protein-kinase C activation (mammals: Davis *et al.*, 1986a, and reviewed by Farese, 1987; amphibians: Kleis-San Francisco and Schuetz, 1988).

The regulation of cAMP levels in the different ovarian compartments warrants further investigation, particularly the chronological aspects, bearing in mind the apparent paradoxical character of its involvement within the follicle at the time of oocyte maturation induction. This requires a cAMP decrease at the oocyte level (see Section III, B, 4), whereas the gonadotropin's maturation surge is supposed to act through an increase of cAMP levels within follicular steroidogenic cells. This paradox is illustrated by the effects on intrafollicular oocyte maturation of high levels of cAMP, artificially elevated *in vitro* by using various substances such as exogenous cAMP or synthetic derivatives, forskolin or cholera toxin (stimulating endogenous cAMP synthesis, through the activation of adenylate cyclase), and methylxanthines (inhibiting cAMP degradation, through the inhibition of phosphodiesterase). In lower vertebrates, such high cAMP concentrations directly promote MIS production or enhance gonadotropin-stimulated MIS production but inhibit the oocyte maturation-inducing effect of MIS. However, transiently high or intermediate cAMP concentrations can stimulate MIS production without inhibiting the oocyte maturation response (amphibians: Kwon and Schuetz, 1985; fish: Jalabert and Finet, 1986; DeManno and Goetz, 1987; Iwamatsu *et al.*, 1987a). The same kind of effects can be observed in mammalian follicles, with minor variations due to species and/or experimental conditions but with the main difference that steroids, which are produced in response to increased cAMP, are not considered as maturation-inducing substances (Ekholm *et al.*, 1984; Racowsky, 1985; Hashimoto *et al.*, 1985; Tsafriri, 1985; Homa, 1988; Dekel *et al.*, 1988a; Hosoi *et al.*, 1989). As a general trend, it appears that the differential regulation of cAMP levels in the

various follicular compartments (intracellular synthesis and degradation and intercellular exchanges) might be one important mechanism controlling the timing of meiosis resumption.

Finally, recent experiments in sheep suggest that a prostaglandin, PGE_2, might also participate in gonadotropin action on intrafollicular oocyte maturation by controlling the expansion of cells of the mural granulosa and cumulus oophorus, thus modulating the possible transfer via cell-to-cell contacts, of intrafollicular substances (Murdoch, 1988).

B. Regulation of Ovarian Steroidogenesis

The precise role of steroids in the regulation of oocyte maturation in mammals is still unknown. However, as discussed above, an adequate balance between the various kinds of steroids is probably necessary for the whole maturation process. More conclusive data were obtained in lower vertebrates, where progestins may be considered as physiological MIS. In both cases, the regulation of steroidogenesis is an important step in the endocrine control of oocyte maturation, particularly when the competence of matured oocytes for subsequent development is considered.

In vitro experiments suggest a synergy between different follicular cell categories, and therefore two-cell type models have been proposed for several species: (1) for the production of androgens by thecal cells from progestins produced by granulosa cells (Fortune, 1986); (2) for the production of estrogens by granulosa cells from androgens produced by thecal cells (Liu and Hsueh, 1986; Young *et al.*, 1982a; Nagahama, 1987c; and (3) for the production of MIS (17α,20β-OH-P) by granulosa layers from 17α-hydroxyprogesterone produced by the thecal layer in salmonids (Young *et al.*, 1986; Nagahama, 1987c; Wright and Zhao, 1988). However, such models are not universal and still too simple. Thus, in some species, thecal cells are able to synthesize estradiol (mammals: Evans *et al.*, 1981; Vernon *et al.*, 1983; birds: Huang *et al.*, 1979; Marrone and Hertelendy, 1983), and aromatase can be detected immunocytochemically in both cell categories (rodents: Matsuda *et al.*, 1984). Furthermore, stromal tissues may also cooperate in ovarian steroid production (McNatty *et al.*, 1980). In the following discussion, experiments performed with various components of the ovary will be considered. Each component may exhibit a specific sensitivity to common nonspecific regulating factors. Furthermore, data from *in vitro* experiments should be interpreted with caution when physiological models of regulation are proposed.

The intrafollicular levels of several steroids, and the regulation of their biosynthesis, have been extensively investigated in many mammals, but accurate information on the oocyte stages in relation to meiosis resumption is often lacking. Moreover, results may be contradictory, depending on the

species, the particular methodology of *in vitro* experiments, the quality and dosage of pituitary hormone preparations used, and the pattern of stimulation.

However, a general phenomenon observed *in vivo* after the gonadotropin preovulatory surge is the increased progestin–estradiol ratio (P–E), even in species in which gestation is absent. This increase is mainly due to, at least within a short period following gonadotropic stimulation, an increase in the production of progesterone (or 17α,20β-OH-P in some teleostean species), which may be amplified by a decrease in estradiol synthesis (Ainsworth *et al.*, 1980; Vanhems *et al.*, 1982; Dieleman *et al.*, 1983; Schenken *et al.*, 1985; Grant *et al.*, 1989). However, a progesterone increase occurs later in some species (ewe: Murdoch and Dunn, 1982). In birds and other nonmammalian vertebrates, this evolution of the P–E ratio occurs well before the initiation of meiosis resumption (birds: Doi *et al.*, 1980; Bahr *et al.*, 1983; Robinson and Etches, 1986; salmonid fish: Fostier and Jalabert, 1986; Van Der Kraak and Donaldson, 1986), and a decrease of estradiol may occur prior to the progestin peak (Fostier *et al.*, 1978). *In vitro*, the steroidogenic response to gonadotropins of follicles taken at various stages of the ovarian cycle show similar patterns (rat: Hillensjö *et al.*, 1976; fowl: Robinson and Etches, 1986; *Xenopus:* Fortune, 1983; trout: Fostier and Jalabert, 1986).

The decrease in estradiol secretion, in relation to the LH surge, may be due to a lower aromatase activity in several mammals (Hillensjö *et al.*, 1977; Dieleman and Blankenstein, 1984; Polan *et al.*, 1984), birds (Armstrong, 1984), amphibians (Mulner *et al.*, 1978), and fish (Young *et al.*, 1983b; Kagawa *et al.*, 1984; De Monès and Fostier, 1987), but this is still controversial. A decrease in androgen production, via a fall in 17α-hydroxylase and C17,20-lyase activities, may also participate in the drop in estradiol secretion (human: Brailly *et al.*, 1981; rat: Suzuki and Tamaoki, 1983; Fortune and Hilbert, 1986; hen: Marrone and Hertelendy, 1985; goldfish: Nagahama *et al.*, 1986). Depending on species, a direct inhibitory effect of LH or of GTH on the activity of aromatase was demonstrated *in vitro* (pig: Tsang *et al.*, 1985; *Xenopus:* Mulner *et al.*, 1978; trout: Sire and Dépêche, 1981; De Monès and Fostier, 1987) and was also demonstrated on the activity of C17,20-lyase (rat: Uilenbroek, 1985). Aromatase was also inhibited *in vitro* by prolactin (Tsai-Morris *et al.*, 1983).

In mammals, FSH and LH enhance progesterone production at various steps of the steroidogenic pathway: uptake of lipoproteins, liberation of cholesterol from lipoproteins, mobilization of cholesterol, conversion of cholesterol into pregnenolone, and conversion of pregnenolone into progesterone (Ireland, 1987). FSH does not retain its stimulatory effect on estradiol secretion by granulosa cells collected during or after the LH peak but retains its capacity to amplify progesterone production (Channing and Reichert, 1984; Fortune and Hilbert, 1986; Quirk *et al.*, 1986). Prolactin, in addition to

the inhibition of estradiol production, may also increase progesterone secretion by granulosa cells (Fortune and Vincent, 1986).

In lower vertebrates, the stimulation of MIS production by gonadotropins has been well documented. Two chemically distinct glycoprotein gonadotropins, GTH I and GTH II, have recently been purified and characterized from chum salmon pituitaries (Suzuki *et al.*, 1988a,b; see Sections II, A, 1 and IV, A, 1). GTH II, which is more similar to tetrapod gonadotropins, was claimed to be more potent than GTH I in stimulating 17α,20β-OH-P production by intact amago salmon ovarian follicles *in vitro* (Suzuki *et al.*, 1988b). In some teleosts it was suggested that 20β-hydroxysteroid dehydrogenase (20β-HSD), the key enzyme converting 17α-OH-P into 17α,20β-OH-P, is induced *de novo* by gonadotropins (Nagahama *et al.*, 1985), but other enzymatic steps are probably involved. The availability of the precursor (17α-OH-P) for 20β-HSD is increased (Kanamori *et al.*, 1988), both through stimulation of its own synthesis at early steps of steroidogenic pathway (Young *et al.*, 1982b; Petrino *et al.*, 1989) and probably through an inhibition of 17-20-lyase (Zohar, 1982; Scott *et al.*, 1983).

The regulation of steroid-transforming enzymes by endogenous steroids themselves is now well established (Gower and Cooke, 1983). Thus, a steroid produced within one particular cell may act on its own synthesis or on the synthesis of another kind of steroid within the same cell, in another ovarian cell belonging to the same category, or in other ovarian cell categories.

Several studies indicate a reversible inhibitory action of estradiol-17β on progesterone secretion by granulosa or thecal cells of mammalian preovulatory follicles, cultured with or without LH (Haney and Schomberg, 1978; Fortune and Hansel, 1979; Hunter and Armstrong, 1987). However, estradiol also exhibits either a long-term (4 days) stimulatory or a short-term (20 h) inhibitory action on progesterone biosynthesis by cultured swine granulosa cells (Veldhuis, 1985a,b). In the former, cholesterol side-chain cleavage and 3β-hydroxysteroid dehydrogenase (3β-HSD) activities were enhanced by estradiol, whereas 3β-HSD was inhibited in the latter. The authors suggested that estradiol might act *in vivo* to limit the premature production of progesterone in developing follicles, while simultaneously "preparing" enzymes for the later production of progesterone. This "preparation" might also occur at the level of low density lipoproteins (LDL) receptors, which are increased by estradiol alone (Veldhuis and Gwynne, 1985) or in synergism with a growth factor, somatomedin C (Veldhuis *et al.*, 1986). Inhibition of progesterone by estradiol has also been reported in birds (Johnson *et al.*, 1988).

In amphibians, estrogens could act directly on the oocyte to inhibit maturation (see Section II, B, 4), but they could also exert an inhibitory effect on gonadotropin-stimulated progesterone synthesis (Lin and Schuetz, 1985a,b). As in mammals, estradiol inhibits 3β-HSD activity in *R. pipiens* ovarian follicles (Spiegel *et al.*, 1978; Lin *et al.*, 1988). Similar results were obtained *in vitro* in fish: inhibition of MIS (17α,20β-OH-P) secretion in trout ovaries

(Jalabert and Fostier, 1984a) and 3β-HSD inhibition in yellow perch ovaries (Theofan, 1981).

Testosterone may enhance progestin secretion in preovulatory follicles of rat (Quirk *et al.*, 1986; Fortune, 1986), chicken (Phillips *et al.*, 1985), and trout (Jalabert and Fostier, 1984a). However, either no effect or even inhibition have also been observed (primates: Bernhisel *et al.*, 1987; Shaw *et al.*, 1989; hen: Johnson *et al.*, 1988).

Intraovarian factors other than steroids were shown to modulate progestin secretion; for example, cAMP, at least as an intracellular relay of gonadotropins (rat: Nordenström *et al.*, 1981; hen: Hammond *et al.*, 1980; frog: Kwon and Schuetz, 1986; rainbow trout: Fostier and Jalabert, 1986; Kanamori and Nagahama, 1988b), opioids (Facchinetti *et al.*, 1986), GnRH-like factors (see Section C), growth factors (reviewed by Carson *et al.*, 1989), follicular inhibin-like activity (Chari *et al.*, 1985), and oocyte maturation inhibitor (OMI) (Hillensjö *et al.*, 1980). Finally, the synthesis of ovarian steroids might be directly controlled by the central nervous system via specific neural pathways (Aguado and Ojeda, 1984). However, further investigations are necessary in order to assign an actual physiological role to these and other factors. For instance, the physiological involvement of prostaglandins in the regulation of steroidogenesis is debatable (Hertelendy and Hammond, 1980; Evans *et al.*, 1983).

In conclusion, whereas the role of gonadotropins in the periovulatory production of steroids is relatively well known, further investigations of the possible role of other pituitary hormones and potential paracrine factors are needed in order to draw a more detailed and pertinent scheme of steroidogenesis regulation at the time of meiosis resumption.

C. Involvement of Ovarian Peptides

At least three kinds of peptides may be of importance for intraovarian paracrine regulation related to the control of meiosis resumption. One is vasoactive intestinal peptide (VIP), known to inhibit a wide range of activities in various cells. VIP was recently located by immunofluorescence in nerve fibers within the stromal and thecal compartments of the rat ovary (Ahmed *et al.*, 1986). It stimulated meiosis of follicle-enclosed rat oocytes *in vitro*, but with a lower efficiency than LH (Carlsson *et al.*, 1987; Törnell *et al.*, 1988). However, its physiological significance remains unclear in all vertebrates. In addition, epidermal growth factor (EGF), insulin-like growth factors (IGFs) and transforming growth factors (TGFs) appear able to stimulate intrafollicular maturation of rat oocytes (Dekel and Sherizly, 1985; Feng *et al.*, 1988).

Another kind of peptide suspected to be involved in the intraovarian regulation of oocyte maturation appears to be related to gonadotropin-releasing hormone (GnRH). Arguments favoring this hypothesis have been provided, so far mainly in mammals, by the observation of direct effects of GnRH on the

ovary, the characterization of ovarian receptors, and the identification of GnRH-like activity within the ovary (see Knecht *et al.*, 1985c, and Cooke and Sullivan, 1985, for review). Although the evaluation of GnRH effects on ovarian functions may depend on various factors such as response criteria, methods, and species, direct effects are essentially inhibitory in immature follicles, with suppressed responsiveness to gonadotropins, whereas stimulatory actions arise in more mature follicles (Knecht *et al.*, 1985c). Thus, GnRH or its agonists promote ovulation in hypophysectomized rats (Ekholm *et al.*, 1981; Corbin and Bex, 1981; Dekel *et al.*, 1985). They promote ovulation in perfused rat ovaries (Koos and LeMaire, 1985), but rabbit ovaries appear much less sensitive (Eisenberg *et al.*, 1984; Koos and Le Maire, 1985). They stimulate the maturation of follicle-enclosed rat oocytes *in vitro* (Hillensjö and LeMaire, 1980) and can improve the proportion of isolated oocytes from the primate *Macaca fascicularis* that undergo GVBD *in vitro* (Lefèvre *et al.*, 1988). Specific receptors were identified in all ovarian compartments in the rat (Séguin *et al.*, 1982). In the rat, ovarian GnRH receptors show some similarities with pituitary receptors with respect to structural properties (Iwashita and Catt, 1985) and the relative potency of various agonists and antagonists (Hsueh *et al.*, 1983). The mechanism of action of GnRH on the follicle leading to oocyte maturation in mammals is not better understood than that of gonadotropins. As with LH, GnRH and its agnonists were found to induce a dosage-dependent stimulation of prostaglandin E, progesterone, and androstenedione by isolated preovulatory rat follicles (Hillensjö *et al.*, 1982; Popkin *et al.*, 1983). Both hormones seem to generate, as an early step of their action on granulosa cells, rapid modifications in the metabolism of membrane phospholipids, leading to the production of IP_3 and DAG (Davis *et al.*, 1986a,b). However, unlike LH, GnRH does not promote any noticeable rise in cAMP level, either within isolated follicles (Hillensjö *et al.*, 1982) or in isolated granulosa cells (Clark *et al.*, 1980; Naor *et al.*, 1984). Moreover, GnRH appears to stimulate cAMP degradation by the membrane phosphodiesterase of granulosa cells (Knecht *et al.*, 1983), an action which could be of importance for the differential regulation of the cAMP level between the oocyte and other follicular compartments at the time of oocyte maturation. Finally, the existence, in the ovary, of GnRH-like peptides was demonstrated in the rat (Ying *et al.*, 1981; Aten *et al.*, 1986), the cow and the ewe (Aten *et al.*, 1987), and in human follicular fluid, where a chemical primary structure was determined (Li *et al.*, 1987). All data demonstrate that ovarian GnRH-like peptides are different from the hypothalamic GnRH.

Few data are presently available concerning the possible involvement of GnRH-like peptides in the intraovarian regulation of oocyte maturation in lower vertebrates. GnRH failed to alter testosterone or progesterone secretion or GVBD, induced *in vitro* by gonadotropins in frog ovarian fragments (Hubbard and Licht, 1985), whereas an agonist analogue of teleost GnRH

reduced the GVBD response of goldfish follicle-enclosed oocytes to gonadotropins, 17α-OH-P, and 17α,20β-OH-P (Habibi *et al.*, 1988). More data are obviously needed in lower vertebrates.

V. REGULATION OF THE HYPOTHALAMO-HYPOPHYSIAL ACTIVITY RELATED TO OOCYTE MATURATION

The "preovulatory surge" of gonadotropins is a signal that initiates a cascade of physiological events beginning with oocyte maturation and leading to ovulation. It results from the mutual adjustment between environmental constraints, integrated by the central nervous system, and the endogenous rhythms of follicular differentiation. We will focus here only on the mechanisms by which follicular differentiation modulates the hypothalamo-hypophysial activity and thus the preovulatory surge through the retroaction of ovarian steroids.

Although various models have been described in different mammalian species, some general trends can be considered. Estradiol seems to be the first ovarian signal to initiate the LH preovulatory surge and, presumably, concomitant FSH release (primates: Knobil, 1980; rat: Goodman and Knobil, 1981). Whereas estradiol negatively modulates the pituitary response to GnRH pulses from the hypothalamus during follicular growth, it finally reaches a high threshold level that induces a positive feedback leading to the preovulatory surge. Progesterone appears also to play an important role in modulating the amplitude and the time of the LH surge (reviewed in Ramirez *et al.*, 1984). This may account for the rise in the hypothalamic GnRH content at proestrus in the rat (Wise *et al.*, 1981) and was shown to induce GnRH release *in vitro* by isolated hypothalamus from mature rat (Rasmussen and Yen, 1983). This action of progesterone seems to require, however, estrogenic priming (Kim and Ramirez, 1985, 1986).

In the hen, increased levels of progesterone (Furr *et al.*, 1973), testosterone (Shahabi *et al.*, 1975a,b; Etches and Cunningham, 1977) and estradiol (Senior and Cunningham, 1974; Shahabi *et al.*, 1975a,b; Shodono *et al.*, 1975) are associated with the preovulatory LH surge. This LH surge was shown in fact to be biphasic: an initial small increase occurs just after the onset of darkness, followed by a subsequent larger preovulatory release (Williams and Sharp, 1978). Converging experimental data have demonstrated that this last main preovulatory surge of LH is induced by a positive feedback effect of progesterone secreted by the largest yolky ovarian follicle, when present, responding to the first small LH peak (Etches and Cunningham, 1976a,b; Williams and Sharp, 1978; Johnson and Van Tienhoven, 1984). The major involvement of progesterone rather than other steroids rising at the same time

was suggested by the complete inhibitory effect of injected progesterone antibodies on ovulation. Estradiol antibodies were not inhibitory, and testosterone antibodies were only partially inhibitory (Furr and Smith, 1975). Estradiol, however, was shown to facilitate progesterone-stimulated LH release (Wilson and Cunningham, 1981) and was suggested to increase hypothalamic and hypophysial concentrations of progesterone receptors (Kawashima *et al.*, 1979a,b). Progesterone seems to act at the pituitary level by increasing LH production but not necessarily spontaneous release, as shown *in vitro* in dispersed cells from hen pituitaries taken at various times during the ovulatory cycle (Kawashima *et al.*, 1982). Furthermore, the pituitary responsiveness to GnRH *in vivo* appears unaffected throughout the preovulatory period (6–24 h) (Bonney *et al.*, 1974). At the hypothalamic level, several indirect observations suggest that progesterone increases GnRH secretion (Tanaka *et al.*, 1974; Fraser and Sharp, 1978; Knight *et al.*, 1984).

In fish, we will only consider the rainbow trout, *Salmo gairdneri*, where sufficient endocrinological data are consistent enough to allow a model to be sketched comparable to that in mammals and birds. An increase in GnRH content of pituitary and brain is observed during the period of GV migration (Breton *et al.*, 1986). *In vitro* experiments show that the secretion of GTH by cultured pituitary cells from fish at the GV migration stage, in response to GnRH administered *in vitro*, is enhanced when these cells are preincubated with 17α,20β-OH-P concentrations in the physiological range of plasma values present before the initiation of oocyte maturation (Weil and Marcuzzi, 1987). It can be hypothesized that the rise of plasma GTH observed before the initiation of maturation (i.e., the preovulatory surge, *sensu stricto*) might be due to an increased pituitary sensitivity to GnRH promoted by a positive feedback of low concentrations of 17α,20β-OH-P secreted by the differentiating ovarian follicles. The further large GTH surge observed during maturation could be due both to the increased pituitary sensitivity to GnRH observed at that stage (Weil, 1981) and to an increased GnRH release (from the neurohypophysial part of the pituitary to the gonadotropic part) as suggested by the overall decrease in pituitary GnRH content observed at the same stage (Breton *et al.*, 1986). Finally, at the time of ovulation, when the levels of both GTH and 17α,20β-OH-P are very high *in vivo*, the pituitary response to GnRH *in vitro* is also very high but can then be decreased by physiological concentrations of 17α,20β-OH-P (Weil and Marcuzzi, 1987), which supports the hypothesis of a negative feedback of 17α,20β-OH-P at that stage (Jalabert *et al.*, 1976; Jalabert *et al.*, 1980b).

From a comparison of data in mammals, birds, and fish, it appears, in general, that ovarian progestins secreted as a result of follicular differentiation play an important role in allowing or even initiating the preovulatory gonadotropin surge and in modulating the evolution of further periovulatory gonadotropin secretion.

VI. ACQUISITION OF MATURATIONAL COMPETENCE

The concept of maturational competence may be extended to any component of the female organism, from the germinal and somatic ovarian cells to any tissue, gland, and organ involved in the production of oocytes with the potential to resume meiosis, to be fertilized and to yield viable embryos. It implies that each component is first able to receive and to translate correctly an external signal (receptivity) within a normal physiological range (sensitivity) and then is capable of giving the appropriate response (responsiveness), which may be the emission of another signal or the realization of the final biological events. Most of our knowledge concerns receptivity and sensitivity levels, which can be evaluated by measurable criteria capable of being stimulated by exogenous stimuli. The actual responsiveness of a biological system is more difficult to predict because morphological or biochemical criteria generally available are only partial indicators in comparison to the complexity of the final response. Finally, correct evaluation of complete maturation is facing a last methodological difficulty: embryonic development, which is the best criterion for such an evaluation, requires factors other than those strictly dealing with oocyte maturation (i.e., relating to adequate fertilization and environmental conditions). The following discussion will focus exclusively on the ovarian competence, considering the follicle and the oocyte level.

A process of recruitment occurs in mammals during folliculogenesis, when a group of preantral follicles becomes responsive and dependent upon gonadotropins. Some of them are selected to grow and become dominant under control of endocrine and intraovarian factors. Ireland (1987) recently reviewed the various factors that could control follicular growth and development. Dominant follicles elaborate factors able to inhibit, within the ovary, the development of other follicles. Besides, they secrete estradiol and inhibin, both of which depress the secretion of FSH, leading to a hormonal milieu inhibiting the growth of other follicles. Since estradiol is necessary for normal follicle growth and granulosa differentiation, attention has been focused on the regulation of aromatase. A protein that inhibits granulosa cell aromatase has been purified from porcine follicular fluid (Ono *et al.*, 1986). It inhibits estrogen secretion by cells from medium-sized follicles but not from large follicles. Dominant follicles could thus secrete enough estradiol to favor their own development and prevent the differentiation of other follicles by inhibiting their estrogen synthesis. During follicular growth, the number of FSH and LH receptors increases (see Section IV, A, 3) and the patterns of steroidogenesis evolve (see Section IV, B). The capacity of the follicle-enclosed oocyte to resume meiosis following exposure to LH is correlated with the responsiveness of granulosa cells to this hormone (Dekel *et al.*, 1988b). Once antral follicles have reached their final size, they become ready

to respond to the preovulatory gonadotropin surge. This, in turn, induces changes in follicular physiology, particularly steroidogenesis, already described (Section V). Besides, follicular environment may prevent oocyte degeneration at this stage (Sato and Ishibashi, 1988).

In lower vertebrates, the follicle size is mainly dependent on oocyte growth (vitellogenesis); poor attention has been paid to the follicular differentiation itself, except in terms of GTH receptor capacity (Kanamori and Nagahama, 1988a; Breton and Sambroni, 1989) and of steroidogenic capability (Nagahama, 1988). Steroid secretion can be stimulated during the whole reproductive cycle by GTH, but the MIS is mainly secreted by postvitellogenic follicles in amphibians (Fortune, 1983) and fish (Young *et al.*, 1983c; Fostier and Jalabert, 1986; Van Der Kraak and Donaldson, 1986; Sakai *et al.*, 1987; Lin *et al.*, 1987; Kanamori *et al.*, 1988). At this stage, the neosynthesis of steroidogenic key enzymes may occur (Nagahama *et al.*, 1985). In coho salmon, both 20β-HSD activity in the granulosa cells and 17α-OH-P secretion by the theca cells are determining factors for the 17α,20β-OH-P surge (Kanamori *et al.*, 1988). However, the way in which this potentiality is acquired by follicular cells is still unknown. Besides, follicular sensitivity to GTH increases during the postvitellogenic stages, evaluated either through the final GVBD response (Jalabert and Fostier, 1984b) or MIS secretion (Fostier and Jalabert, 1986). This evolution is associated with that of plasma GTH profiles (Zohar, 1982; Zohar *et al.*, 1986). Continuous exposure of follicles to GTH seems necessary to obtain a maturational steroidogenic response (Zohar, 1982; Zohar *et al.*, 1986). GV migration to the oocyte periphery has been positively correlated with this increase in sensitivity (Jalabert and Fostier, 1984b). The ovarian sensitivity to GTH may be repressed by follicular factors, among which estradiol is a possible candidate (see Section IV, B), whereas these follicular factors themselves may be depressed by low priming levels of GTH. Thus, the percentage of GVBD after coculture of carp ovarian fragments from primed females (injected with a low dose of carp pituitary homogenate) with ovarian fragments of unprimed females is decreased in comparison with cultured fragments from primed fish alone (Kime *et al.*, 1989).

Concerning the oocyte itself, the term *competence* has been used for two kinds of phenomena: (1) Developmental competence is the ability to undergo fertilization and embryonic development after meiosis resumption (Staigmiller and Moor, 1984). In many mammalian species, this ability may be acquired only after the initiating action of GVBD-inducing factors and even after GVBD. It needs the action of factors, probably including steroids originating in the granulosa cells (see review by Thibault *et al.*, 1987, and Section II, A, 1), and requires direct cell–oocyte contacts to be effective (Mattioli *et al.*, 1988a,b). In the fish *O. latipes*, the arousal of developmental capacity also requires factors from the follicular cells (Iwamatsu and Ohta, 1981). (2) Meiotic competence is the ability to resume meiosis when the

follicular inhibitory action is suppressed (mammals) or when specific MISs are provided (lower vertebrates) (Thibault, 1977). We will focus here on meiotic competence. This is an intrinsic characteristic of the differentiated oocyte, even though its differentiation has been obtained with the necessary help of cooperating follicular cells (Thibault *et al.*, 1987). Thus, studies on the blockage of spontaneous intrafollicular maturation in *R. pipiens* show that the higher sensitivity to progesterone induction observed in follicles from animals around the natural breeding season (spring) in comparison to follicles from winter frogs is probably related to a different balance between negative and positive hormonal control and not to a different oocyte sensitivity (Lin and Schuetz, 1985b). Such data show that the evaluation of the actual oocyte competence is necessarily difficult since, in all species, the follicular cycle is a dynamic process during which the levels of all endocrine and paracrine factors are continuously varying until ovulation. Therefore, meiotic competence should theoretically be evaluated independently of its complex environment.

In mammals, meiotic competence is acquired only around the period of antrum formation, when the oocyte reaches 80 to 90% of its final size (Thibault *et al.*, 1987). However, the oocytes from juvenile animals are generally incompetent to resume meiosis, even if they come from antral follicles (reviewed by Thibault, 1977; Moor and Warnes, 1978). The ability to resume meiosis spontaneously in culture is not acquired until the age of 15–21 days pospartum (pp) in mice, 23 days pp in hamster, and 20–26 days pp in rat (Tsafriri *et al.*, 1983). Meiotic competence, abolished after hypophysectomy in the rat, is restored by FSH but not by LH. Restoration appears to require steroid synthesis since it is prevented by steroidogenesis inhibitors (Bar-Ami *et al.*, 1983). Thus, the completion of RNA accumulation during oocyte growth could be a prerequisite for the acquisition of competence (Moor and Warnes, 1978; Moore and Lintern-Moore, 1974). Treatments with pregnant mare serum gonadotropin (PMSG) or estradiol are effective in restoring oocyte competence when administered between 25 and 31 days pp in rat hypophysectomized on day 15 pp, but they are ineffective prior to 25 days pp. The time at which hormonal replacement can restore meiotic competence corresponds to the age at which competence is normally acquired, and this timing suggests an essential role of age-dependent differentiation of the ovary (Bar-Ami and Tsafriri, 1986).

In lower vertebrates, only indirect conclusions can be drawn from experiments performed on fish oocytes, since they were usually cultured within their follicles. Oocyte sensitivity to MIS may be acquired early in *F. heteroclitus*, at a smaller size than that of oocytes undergoing spontaneous maturation *in vivo* (Wallace and Selman, 1978). However, the sensitivity of oocytes gradually increases when they are collected closer to the natural spawning time, when follicular size is still increasing (Begovac and Wallace, 1988), or, in some species, when GV peripheral migration is occurring (Goetz and

Theofan, 1979; Jalabert and Fostier, 1984b; Goetz and Cetta, 1985; Lutes *et al.*, 1987). Such evolution can exhibit very short, one-day cycles in daily spawning fish (Iwamatsu, 1974; Kobayashi *et al.*, 1988). This increase in sensitivity seems to be correlated with an overall increase in intraoocyte basal levels of cAMP (Jalabert and Finet, 1986). More data are available on amphibians. Denuded oocytes are sensitive to MIS at a smaller size than those able to respond *in vitro* to hCG inside their follicle (Reynhout *et al.*, 1975). However, smaller oocytes unresponsive to progesterone undergo GVBD when microinjected with MPF. Further analysis showed that this lack of a response by small oocytes might be due to less receptors to MIS and to a deficiency in an event(s) subsequent to cAMP relay and prior to MPF action (Sadler and Maller, 1983). These studies demonstrate that intrinsic oocyte differentiation is required before the successful initiation of maturation and involves various cellular processes.

VII. CONCLUDING REMARKS AND BIOMEDICAL IMPLICATIONS

Numerous works on the endocrinological, cellular, and molecular mechanisms regulating oocyte maturation in mammals have been directly stimulated by the need to improve human fertility control and fecundity in domestic mammals. The principal applications concern the control of ovulation *in vivo* and the identification of oocyte maturation quality markers for *in vitro* maturation and fertilization (reviewed by Pellicer *et al.*, 1987, in human).

From a more general point of view, oocyte maturation represents an important phase of female meiosis, which may be considered as a particular case of the general process of cell division, subject to multiple stop–go controls (Lindner *et al.*, 1980). These controls involve a number of intracellular factors, such as MPF and cytostatic factors (Masui, 1985), and several external chemical or physical factors acting as specific signals inducing the first and second meiotic divisions. Data in this field may provide valuable information about the fundamental mechanisms of cell proliferation and, therefore, are of considerable biomedical interest.

For example, MPF was first discovered in the cytoplasm of amphibian oocytes resuming meiosis (see Section III, A). It subsequently turned out to be an important regulation factor, involved in the control of all kinds of cell division (not only meiotic but also mitotic). Thus, it was found in the cytoplasm from unfertilized eggs and synchronously cleaving embryos (Reynhout and Smith, 1974; Wasserman and Smith, 1978; Gerhart *et al.*, 1984; Dettlaff and Ryabova, 1986) and in synchronously dividing cultured somatic cells (Sunkara *et al.*, 1979; Nelkin *et al.*, 1980). MPF is not even restricted to vertebrates, since it was found in other eukaryotes such as yeast (Weintraub *et al.*, 1982) and the slime mold *Physarum polycephalum* (Adlakha *et al.*,

1988). Its recent characterization (see Section III, A), which is due to the convergence of molecular genetic and cell biology approaches, opens fascinating perspectives to understanding the general mechanisms regulating the cell cycle (reviewed by Murray, 1989).

Another example comes from the observation that several proteins, first identified as oncogene products of transforming genes, are able to interfere in the cellular transduction of meiosis-inducing signals and may normally participate in the control of cell multiplication. This is the case for the p21 *ras* protein, which induces GVBD when microinjected in *X. laevis* oocytes (Birchmeier *et al.*, 1985), appearing as a potential mediator of insulin action (Korn *et al.*, 1987; Deshpande and Kung, 1987). This is also the case for the *c-mos* proto-oncogene product, which is detectable only during progesterone-induced maturation in *Xenopus* oocytes, whereas its specific antisense oligonucleotide blocks GVBD (Sagata *et al.*, 1988).

All the above data have been obtained by the convergence of both cellular and molecular biology approaches initially performed in lower vertebrates. From another point of view, it must also be underlined that the identification of maturation-inducing steroids in lower vertebrates has been encouraging reinvestigations into the role of steroids in mammalian oocyte maturation (Tesarik, 1986).

Even if the primary interest of such works is in the human, the use of "model systems" in animals is required because of ethical considerations and organ availability (Lindner *et al.*, 1980). Besides, although mammalian models have been extensively used, they present some technical limits, such as the small size and the low number of synchronous oocytes available from the ovaries of one donor female. In contrast, many amphibian and fish species are characterized by the availability, at the end of the reproductive cycle, of numerous and large oocytes at the same stage of development (3,000/1 kg in rainbow trout; 20,000 in northern pike; and 100,000 in common carp). While oocyte diameter in eutherian mammals ranges between 60 and 150 μm (Thibault *et al.*, 1987), it can reach 1.3 mm in amphibians and 6–8 mm in salmonids as a result of the yolk volume. Manipulations with forceps, microinjections, and microsurgery are thus much easier with such oocytes (Hitchcock and Friedman, 1980). The availability of a large number of synchronous oocytes or follicles from only one donor female can be used to eliminate the problem of variations among individuals in sensitivity levels. This was used to set up various kinds of *in vitro* bioassays: some homologous gonadotropin assays have been using the GVBD response of oocytes within cultured follicles from *Xenopus* (Thornton, 1971), rainbow trout (Jalabert *et al.*, 1974) and *Fundulus* (Lin *et al.*, 1987), whereas a heterologous assay for porcine and human OMI has been developed using the inhibition of the GVBD response of progesterone-stimulated oocytes from *Xenopus* (Cameron *et al.*, 1983; Pomerantz and Bilello, 1987). The initial discovery of MPF, and the assessment of its main properties, was made possible by the

GVBD response of living amphibian oocytes microinjected with cytoplasmic extracts (Dettlaff *et al.*, 1964; Masui and Markert, 1971). The same bioassay has been used to confirm the involvement of cyclin as a possible activator of MPF (Swenson *et al.*, 1986) and to assess the activity of highly purified MPF preparations. Final MPF identification and characterization succeeded thanks to a still more sensitive, cell-free assay using cytoplasmic extracts from *Xenopus* oocytes (see Section III, A). Finally, a low molecular weight factor active on fish intrafollicular oocyte maturation has been found in chicken and rabbit steroid-free sera and deserves further investigations (Iwamatsu *et al.*, 1987b). The large number of eggs available could also be used to screen the toxic and teratogenic effects of various chemicals or medications, which could be fortuitously used during the process of oocyte maturation (Armstrong, 1986) or which are administered in order to cause or facilitate ovulation in infertile women (Scialli, 1986; Yun *et al.*, 1987).

A number of other features of lower vertebrates may be of interest for various experimental purposes. The follicular morphology seems to offer a simpler model because of the absence of cumulus cells (granulosa cells are directly in contact with the oocyte) and of antral cavity. Due to poikilothermy, physiological experiments can be performed over a wide temperature range, and extreme levels can even be used. This may be done in order to define precisely optimal and limiting temperatures for various physiological mechanisms (Iwamatsu and Fujieda, 1977; Epler *et al.*, 1987) and should be considered as a possible tool for simulating and understanding phenomena such as the heat stress in mammals, responsible for decreased reproductive performances in domestic mammals (Baumgartner and Chrisman, 1987). From a more general point of view, lower vertebrates can provide very suitable models for studying the role and mechanism of action of all kinds of external factors.

From the present review, it becomes apparent that many features of the endocrinological and cellular regulation of oocyte maturation are common to all vertebrates. The great interest in lower vertebrate models has been particularly well demonstrated by several discoveries ultimately extended to mammals. This is the case for MPF, first discovered in amphibians and teleosts before its ubiquity was further demonstrated (see Section III, 1). This is true also for the central role of cAMP and of some of the mechanisms of its regulation in the oocyte. From a general point of view, the suggestion that binding on the external membrane is the first step of progesterone action on the amphibian oocyte raised new interest about the role of the interaction of steroids with the plasma membrane as a more general mechanism of their action on other cell targets in all vertebrates (Szego and Pietras, 1981).

Taking into account the general interest of research on the regulation of oocyte maturation performed on lower vertebrate models, many fields of investigation remain open now, and some challenging problems can be briefly listed:

1. Identification and purification, in addition to MPF and cyclin, of other cytoplasmic factors involved in the control of the cell cycle
2. Characterization of the various cellular mechanisms extending from the external stimulation to the activation of MPF
3. Identification of follicular factors that participate in the acquisition of meiotic and developmental competence
4. Identification and mechanism of action of factors that inhibit the maturation of already competent oocytes
5. Comprehension of mechanisms involved in the ageing of mature oocytes
6. Identification of the MIS in species belonging to various orders and classes
7. Respective role of endocrine and paracrine controls on MIS production
8. Modulation of MIS activity by other steroids
9. Mechanism of action of MIS at the membrane and cytoplasmic levels (the question of whether the external membrane is the only oocyte target of MIS action in lower vertebrates is of particular interest regarding the role of steroids in the acquisition of developmental competence in mammals)
10. Knowledge of extraovarian functions of MIS, which appears to be involved in the coordination of various aspects of reproductive activity, not only as an endocrine messenger but also as a putative pheromone in certain fish species (Sorensen *et al.*, 1987; Stacey *et al.*, 1989);
11. Comprehension of the nature of intrafollicular regulations involved in the chronological link between maturation and ovulation
12. Understanding of the biological integration of environmental cues

As shown in the present chapter, some of the best model systems for solving these problems can be found in amphibians and fish. However, more work should also be performed on reptiles and birds, so that a comparative survey may bring out general evolutionary trends and improve our understanding of the mammalian model.

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