Roles of activin and its signal transduction mechanisms in reproductive tissues

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Activins were identified initially as gonadal proteins having a stimulating effect on FSH production by the pituitary gland. Strong evidence has accumulated that activins are important regulating factors for many reproductive processes. Activin may have paracrine or autocrine roles rather than solely an endocrine action on FSH secretion. Activins together with their signalling molecules must be shown to be produced locally in a particular tissue to provide support for their paracrine or autocrine action in that tissue. The discovery of the activin receptors, the intracellular signalling mediators (Smads) and some transcription co-factors involved in activin responses has helped to unravel the activin–transforming growth factor β signalling mechanism. However, few reports have clearly demonstrated the presence of all of the activin signalling molecules in reproductive tissues, despite the important roles of activin in these tissues. Several activin receptor types and Smad molecules have been identified, indicating either a redundancy in signalling molecules or different signalling pathways. At present, it is not clear which particular subset of these signalling molecules is important in reproductive processes. The aim of this review is to collate the information available on activin actions, as well as on the signalling molecules, to understand how activins may transduce their paracrine or autocrine signals in reproductive tissues.

The discovery of many cytokines and differentiation factors in recent years has stressed the importance of paracrine and autocrine activities in reproduction. Among these molecules, activins are of prime importance. Discovered in 1986 (Mathews, 1994), many studies have since demonstrated that activins are involved in the regulation of several reproductive processes in higher vertebrates. The biologically active form of activin is composed of two β-subunits covalently attached by a single disulphide link. So far, five β-subunits have been identified (βA to βE) (Woodruff, 1998), but only the βA- and βB-subunits have been shown to dimerize, giving three possible types of activin species (Fig. 1), which are named according to the subunit species of which they are composed (activin A, B and AB). The βA- and βB-subunits can also heterodimerize with the related α-subunit to form the activin antagonist inhibin. The activin–inhibin subunits are structurally related to the transforming growth factor β (TGF-β) family of peptides, which also includes bone morphogenetic proteins (BMP), Müllerian inhibiting substance (MIS) and growth and differentiation factors (GDF) (Kingsley, 1994). This review concerns the information available on how activins may transduce their signals in reproductive tissues. Owing to an abundance of reports, it is not possible to provide an exhaustive list of activin actions. Nevertheless, the actions most relevant to this review are first discussed, and then the distribution of activin and its signalling components in these tissues are described to demonstrate the presence of a functional activin signalling pathway.

Roles of activins in reproductive processes

Roles of activins in the female

Originally, activins were regarded as acting mainly in the gonadal–pituitary axis since they were identified as gonadal proteins capable of positive regulation of pituitary FSH secretion. Several studies have since confirmed this activity on FSH production as well as on other pituitary produced proteins, such as follistatin (Phillips and de Kretser, 1998; Woodruff, 1998).

Subsequently, the quest for factors regulating folliculogenesis has led to the observation that activins may be important intraovarian regulators (Findlay, 1993). It is now accepted that activin can modulate many ovarian cell functions, at least in vitro. One of the critical steps during folliculogenesis is the acquisition of FSH responsiveness by the follicles. It has been demonstrated, using diethylstilboestrol-treated immature rat granulosa cells, that activin A potentiates FSH-stimulated aromatase activity, as
well as progesterone and inhibin production (Findlay, 1993). The increase in FSH sensitivity is not due to a change in FSH receptor affinity but rather to an increase in FSH receptor mRNA (Nakamura et al., 1993) as well as in the number of FSH receptors at the cell surface (Findlay, 1993). When administered alone, the effect of activin on gonadotrophin receptors is selective to the FSH receptor but, in the presence of FSH, activin A increases the FSH-driven expression of the LH–hCG receptor mRNA (Kishi et al., 1998). Activin A can also have a mitogenic effect on these immature granulosa cells as demonstrated by an increase in \textsuperscript{3}H\textsuperscript{thymidine} uptake. FSH administered alone had no effect on DNA replication, but it becomes mitogenic when administered with activin A (Miro and Hillier, 1996). These data indicate that activin A may have a role in controlling the proliferation and maturation of granulosa cells.

Many studies have further demonstrated that activin A has a direct effect on the synthesis of various ovarian hormones. For example, cultured granulosa cells from immature rats increase their inhibin \(\alpha\)-subunit mRNA and protein biosynthesis in the presence of activin (LaPolt et al., 1989). In contrast, in human granulosa–luteal cells, activin A does not affect the \(\alpha\)-subunit mRNA or the \(\beta\_A\)-subunit steady state concentrations, but it can increase the amount of \(\beta\_B\)-subunit mRNA (Eramaa et al., 1995). Activin A can also modulate steroidogenesis, as demonstrated by the decrease of progesterone secretion by bovine preovulatory granulosa cells (Shukovski and Findlay, 1990) and by the decrease in hCG-stimulated progesterone secretion in human granulosa cells (Woodruff, 1998). Activin also acts on theca cells to inhibit LH-induced androgen production (Findlay, 1993) and on oocytes to enhance their maturation (Alak et al., 1998).

The effect of activin A on cultured follicles has been studied and it has been found that, in addition to a growth-stimulating effect on follicles from immature animals (Liu et al., 1998), activin A promotes the reorganization of follicular structures in the presence of FSH \textit{in vitro} (Li et al., 1995). However, this growth-promoting action seems to be age-specific since it has been shown that activin A cannot increase the size of follicles from adult animals (Liu et al., 1999). In fact, activin A blocks the FSH-induced growth of preantral follicles from adult mice (Li et al., 1999; Mizunuma et al., 1999). It has been further demonstrated that follistatin can block the dominance of secondary follicles on small preantral follicles, indicating that activin from secondary follicles causes small preantral follicles to become dormant (Mizunuma et al., 1999).

\subsection*{Roles of activins in the male}

Activins appear to be as important for male as they are for female reproductive processes (Risbridger and Cancilla, 2000). For example, activin A stimulates proliferation of testicular cells from immature rats (Boitani et al., 1995). However, as they appear to be in female gonads, activin actions on testicular cells are age-specific. In the presence of FSH, activin A stimulates the proliferation of Sertoli cells from 9-day-old rats but not from 18-day-old rats (Boitani et al., 1995). Another study that used transgenic mice overexpressing the \(\beta\_A\)-subunit mainly in the testis indicated that the control of the expression of the \(\beta\_A\)-subunit is critical for male gonadal functions (Tanimoto et al., 1999). In this study, the transgenic mice became infertile, probably as a result of a deficiency in spermatogenesis. However, since the testes produce the \(\alpha\)-subunit together with the \(\beta\_A\)-subunit, it is not clear whether this sterility was due to an excessive amount of inhibin or activin.

Most of the data on activin actions described above have been collected using activin A. It remains unknown whether activin B and AB possess the same activity for the biological effects described in this review. Nevertheless, the few existing data on the activity of activin B indicate that it is...
similar to that of activin A (Corrigan et al., 1991), although this remains to be confirmed.

**Expression of activins in reproductive tissues**

Sites of activin production are widespread and often overlap with their sites of action, leading to the hypothesis that activins have paracrine or autocrine actions in reproduction. Consistent with this hypothesis, circulating amounts of activin A vary only slightly during the menstrual cycle (Muttukrishna et al., 1996), in contrast to inhibit concentrations, which fluctuate over the cycle (Woodruff, 1998). In addition, the changes in serum activin concentrations with age do not correlate with changes in FSH concentrations, and the circulating activin A is sequestered by binding proteins such as follistatin, which may decrease its bioavailability (Loria et al., 1998).

**Pituitary gland**

Early studies have localized the inhibin and activin subunits in the pituitary. One of these studies has shown that the \( \beta _B \)-subunit is detected in gonadotropes while the \( \beta _A \)-subunit was not immunodetected, suggesting that the pituitary produces mainly activin B or inhibin B (Roberts et al., 1989). However, a study on human pituitaries showed that the activin A dimer was present, but mainly in somatotrophs (Wada et al., 1996).

**Ovary**

In the human ovary, the \( \beta _A \)-subunit mRNA is found in the granulosa and theca cells of dominant follicles and in the corpus luteum. In the small antral follicles, a weak expression was also observed in granulosa cells, but not in theca cells (Roberts et al., 1993). \( \beta _A \)-subunit protein has been mainly detected in granulosa cells (Yamoto et al., 1992) and occasionally in theca cells of small antral follicles, despite the absence of its mRNA (Roberts et al., 1993). Roberts et al. (1993) also reported the detection of \( \beta _A \)-subunit in luteal cells. The production of the \( \beta _A \)-subunit in primordial and preantral follicles does not appear to be modulated during the menstrual cycle. However, in medium antral follicles and prevulatory follicles, the production of the \( \beta _A \)-subunit appears to be cycle-dependent, since it was mainly immunodetected during the midfollicular and late follicular phases, respectively (Yamoto et al., 1992). Unfortunately, Yamoto et al. (1992) did not give any information on whether the granulosa cells use the \( \beta _A \)-subunit to produce inhibin A or activins. A study designed to clarify this issue used an anti-activin A antibody with relatively low crossreactivity for inhibin and demonstrated that activin A is present exclusively in the granulosa cells of mature follicles and in the corpus luteum (Wada et al., 1996).

The distribution of expression of the \( \beta _B \)-subunit gene in the ovary is significantly different from that of the \( \beta _A \)-subunit gene. In contrast to the \( \beta _A \)-subunit mRNA, the \( \beta _B \)-subunit messenger is present in high abundance in the granulosa cells of small antral follicles, but was below detection in dominant follicles (Roberts et al., 1993). This switch of \( \beta _B \)-subunit expression may indicate that the \( \beta \)-subunits have different roles to play during the maturation of the follicle. However, a switch in \( \beta \)-subunit expression does not necessarily indicate a change in the type of activin formed. The ovary is a major source of inhibin A and B, the serum concentrations of which change during the menstrual cycle, indicating that the change of subunit expression may reflect a switch in inhibin rather than activin species production. However, Yamoto et al. (1992) could not detect any major difference in the distribution of the \( \beta _A \) and \( \beta _B \)-subunit proteins. Both peptides had the same cycle-independent distribution in primordial or preantral follicles and showed a similar cycle-dependent distribution in small antral and dominant follicles. Thus, it remains unclear whether activin A and B have different roles during folliculogenesis.

**Testis**

In adult rat testes, the mRNAs encoding the \( \beta \)-subunits were localized in the Sertoli cells and their expression was dependent on the seminiferous epithelial cycle. The \( \beta _A \)-subunit mRNA starts to appear at stage VIII, reaching a maximum at stages IX–XI, whereas maximum \( \beta _B \)-subunit mRNA concentrations are observed at stage XIII (Kaipia et al., 1992). However, despite the presence of its mRNA, the \( \beta _A \)-subunit protein was not detected in the rat testes, although, in men, the activin A dimer was detected in Leydig and Sertoli cells (Wada et al., 1996).

The protein distribution and the developmental expression of \( \beta _B \)-subunits in the testes appear to be different from those of the \( \beta _A \)-subunit, at least in rats. During development, \( \beta _A \)-subunit synthesis was immunodetected in fetal Leydig cells but the signal decreased markedly after birth, whereas the \( \beta _B \)-subunit was detected in the Sertoli cells and its abundance increased after birth (Majdic et al., 1997), indicating different roles for the \( \beta \)-subunits during the testicular maturation.

**Endometrium**

In the early stages of the menstrual cycle, the \( \alpha \) and \( \beta \)-subunits were detected in the human endometrium, primarily in glandular epithelium (Leung et al., 1998; Otani et al., 1998; Jones et al., 2000). During early pregnancy, the endometrium also produces all three inhibin–activin subunits (Otani et al., 1998; Jones et al., 2000). The \( \beta _A \) and \( \beta _B \) subunits were also detected in a subset of uterine leukocytes and expression of \( \alpha \)- and \( \beta \)-subunits in decidualized stromal cells was upregulated after the onset of decidualization (Jones et al., 2000). These data imply a role for inhibin or activin in decidualization but the exact physiological roles of activin A in the uterus and in pregnancy remain obscure. However, there is an interesting correlation between circulatory concentrations of activin A and pregnancy. During pregnancy, activin B is generally...
absent from the maternal circulation, but circulatory concentrations of activin A increase to tenfold higher than the menstrual cycle concentrations (Petraglia et al., 1994; Muttukrishna et al., 1996). Furthermore, serum activin A concentrations are significantly higher in women undergoing spontaneous labour compared with women undergoing elective caesarean section, indicating a role in human parturition (Petraglia et al., 1994). This increase in activin A is probably due to its synthesis by decidual and placental tissues rather than by corpora lutea (Otani et al., 1998).

### Signalling mechanisms

Activins are secreted proteins and, as for any external stimulus, responsive cells must bear the proper mechanism to transduce the activin signal intracellularly. Since the cloning of the first cDNA encoding the activin type II receptor a decade ago, a tremendous amount of knowledge has been acquired about the signalling mechanisms of many members of the TGF-β family.

Like most members of the TGF-β family, activins mediate their actions by binding to a complex of transmembrane serine and threonine kinase receptors. So far, four activin receptors have been identified by their ability to bind activin. These proteins can be classified into two main categories, namely the type I receptor group, comprising the activin receptor-like kinase ALK2 and ALK4, and the type II receptor group, comprising the activin type II and type IIB receptors (ActRII and ActRIIB) (Mathews, 1994; Hoodless and Wrana, 1998). In addition, five isoforms of ActRIIB, generated by alternative splicing of its mRNA, have been identified in mice and bovine species (Attisano et al., 1992; Ethier et al., 1997). Thus, activins have the potential to act through several forms of receptors. In fact, to transmit its signal into the targeted cells, several studies indicate that activin must act through a receptor complex made of type I and type II receptors. It is thought that activin binds first to an activin type II receptor, and then an activin type I receptor is recruited into the complex (Fig. 2a). The formation of this ligand–receptor complex induces the activation of the type I receptor by the kinase activity of the nearby type II receptor (Mathews, 1994).

Once activated, the kinase of the activin type I receptor stimulates the downstream pathways. The only direct substrates identified to date form a novel family of proteins called Smads. These proteins can be grouped in three subclasses: the receptor-activated Smads, the common Smads and the inhibitory Smads. Activin can signal specifically through Smad2 and Smad3. Once Smad2 or Smad3 are activated by phosphorylation, they associate with Smad4 and the dimer migrates to the nucleus. The Smad complex can then bind to specific promoters and associate with transcriptional co-factors and co-activators to induce a transcriptional response (Massague and Chen, 2000).

Specific roles, in terms of activin actions, for the different activin receptors are not clear at present. Nevertheless, the creation of activin receptor-deficient mice showed that the type II and type IIB receptors may be functionally different, not only during embryogenesis but also for the maintenance of fertility. The majority of the ActRIIB-deficient mice died soon after birth, but some survived and both males and females were shown to be fertile (Oh and Li, 1997), indicating that an ActRIIB-derived signal is not essential for reproductive processes. In contrast, most of the ActRII-deficient mice were viable but their reproductive ability was impaired. For example, the males had reduced testicular size and their attainment of reproductive maturity was delayed, while the females were infertile, probably owing to a block in folliculogenesis (Matzuk et al., 1995). Nevertheless, the finding that the ActRII-deficient males were fertile indicates that the ActRII-mediated signal is not critical for spermatogenesis. In both male and female ActRII knock-out mice, the FSH concentrations were decreased compared with control mice, indicating that the impairment in fertility may be the result of low concentrations of FSH. This finding also indicates that the signal transduced through ActRII in the gonadotropes is essential to maintain the FSH concentrations and cannot be replaced by an ActRIIB-mediated signal. This functional divergence between ActRII and ActRIIB may be explained by the activation of separate pathways leading to different transcriptional outcomes. However, it is also possible that ActRII and ActRIIB transduce a similar signal but that their distribution may not overlap in regions important for FSH regulation, explaining why ActRII cannot rescue an ActRII deficiency. The targeted disruption of the genes encoding the activin type I receptors ALK2 (Gu et al., 1999) and ALK4 (Gu et al., 1998) and the various Smads (Nomura and Li, 1998) clearly indicates that they are important embryogenic

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<th>Subclass</th>
<th>Signalling specificity</th>
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<td>Receptor-activated</td>
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<td>Smad1</td>
<td>BMP</td>
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<td>Smad2</td>
<td>Activin and TGF-β</td>
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<td>Smad5</td>
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<td>Smad8</td>
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<td>Common</td>
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<td>Smad4</td>
<td>Necessary for activin, TGF-β and BMP signalling</td>
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<td>Inhibitory</td>
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<td>Smad6</td>
<td>Preferentially BMP</td>
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<td>Smad7</td>
<td>Preferentially activin and TGF-β</td>
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Mammalian Smads are clustered in three groups according to their functional characteristics. The receptor-regulated Smads respond to a specific external signal. BMP: bone morphogenetic protein; TGF-β: transforming growth factor-β.
Expression of activin receptors in reproductive tissues

Activin receptors in the ovary

Distribution analysis using 125I-labelled activin A showed that activin A accumulates mainly in the ovary, the pituitary, the testis and the bone marrow in immature and adult rats, indicating the presence of activin receptors in these tissues (Mathews, 1994). Further ligand binding studies in situ in the ovary showed that activin binding to the granulosa cells during all phases of the rat ovarian cycle, as well as to the theca cells of developing follicles, while the corpus luteum showed 125I-labelled activin binding during metoestrus and dioestrus (Woodruff et al., 1993). Consistent with these activin-binding studies, expression of the activin receptors genes has been detected in the ovary. Northern blotting and RT–PCR detected ALK2 and ALK4 mRNAs in granulosa–luteal cells of human ovaries (Erama et al., 1995a; Peng et al., 1999). In the rat ovary, in situ hybridization studies showed that ALK2 mRNA was localized mainly in the oocytes of preantral and antral follicles, but, in contrast to the situation in the human ovary, the ALK4 mRNA was not detectable (He et al., 1993), indicating a species difference or a lack of sensitivity with the in situ hybridization technique used in the rat study. Much more information is available on the gene expression of both activin type II receptors. Northern blotting showed that the mRNAs encoding ActRII and ActRIIB were seen in the bovine and rat corpus luteum (Cameron et al., 1994; Ethier et al., 1994, 1997). Another study showed the presence of ActRII mRNA in ovaries of immature, cyclic and pregnant rats (Feng et al., 1993). In situ hybridization studies have localized a strong signal for the ActRII mRNA over the oocytes as well as a moderate signal in granulosa cells (Cameron et al., 1994). In the human ovary, the available data are inconsistent since ActRII mRNA was detected in the granulosa-luteal cells in an RT–PCR study (Peng et al., 1999) but not in a study using the in situ hybridization technique (Roberts et al., 1994). The localization of expression of the ActRIIB gene is also unclear. Some studies have detected the messenger in the oocytes and in the granulosa cells (Cameron et al., 1994; Erama et al., 1995; Peng et al., 1999) whereas other studies failed to detect it (Aloi et al., 1997; Roberts et al., 1994).

Since the activin subunits have a cycle-dependent distribution in antral follicles and since activin has been demonstrated to affect follicular growth and FSH sensitivity, a modulation in the expression of the activin receptors might be expected to occur during the ovarian cycle. Unfortunately, at present, no reports are available on the modulation of the activin receptor gene expression during the ovarian cycle. Nevertheless, most of the data collected to date tend to indicate that the amounts of activin receptor mRNA can vary during the oestrous cycle in rats, especially in granulosa and luteal cells. For example, amounts of ALK2 and ActRII mRNA have been shown to be modulated during the rat oestrous cycle, increasing during the dioestrous phase (Cameron et al., 1994) and decreasing after the pro-oestrous gonadotrophin surge (Aloi et al., 1997). In contrast, in the oocytes, the amount of ActRII mRNA remained very high regardless of the stage of folliculogenesis or oestrous cycle.

Activin receptors in the testis

Much less is known about the expression of the activin receptors in the testes. The ALK2 gene is expressed in bovine testes, and there is a change in messenger species profile during testicular maturation (J-F. Ethier, unpublished). The ActRII mRNA has been detected in whole bovine and mouse testes by Northern blot analysis (Ethier et al., 1994; Wu et al., 1994). In rats, at the cellular level, ActRII appears to be expressed mainly in spermatogenic cells and, depending on the study, the ActRII mRNA is present at a very low level or absent in Sertoli cells (Kaipia et al., 1992; Cameron et al., 1994). The ActRIIB mRNA was also detected in bovine and mouse testes (Wu et al., 1994; Ethier et al., 1997) but its cellular localization is unclear.
Fig. 2. Model of the signalling mechanism of activin and of its regulation. (a) Signalling mechanism: activin binds to the activin type II receptors, which in turn recruit and phosphorylate the type I receptors. The activin type I receptors transduce the activin signal by phosphorylating the activin–TGF-β-specific Smad2 or Smad3. Once phosphorylated, Smad2 or Smad3 dimerizes with the common Smad, Smad4. The dimer is then translocated into the nucleus, where it associates with cell-specific transcriptional co-factors. The Smad complex can bind directly to the activin response elements (ARE) of activin responsive promoters. It has been suggested that the Smad complex can
since one study detected the ActRIIB mRNA mainly in Leydig and interstitial cells (Cameron et al., 1994) while another localized it in type A1 and A2 spermatogonia and in Sertoli cells (Kaipia et al., 1993).

**Activin receptors in the pituitary**

In correlation with the action of activin on FSH secretion, the mRNAs for ActRI and ActRIIB have been detected in bovine and rat pituitary (Cameron et al., 1994; Ethier et al., 1994, 1997). The ActRIIB mRNA appears to be associated with gonadotropes in prepubertal rats (Wilson and Handa, 1998).

**Expression of intracellular mediators of the activin signal**

A cell needs to be equipped with the complete intracellular machinery involved in activin signalling to be responsive to activins. The information available on the distribution of the Smad proteins in reproductive tissues is extremely limited. The Smad2 protein has been reported to be present in hen granulosa cells at different stages of follicular development, with maximum concentrations occurring during the early stages of folliculogenesis (Li et al., 1997). The Smad2 mRNA has also been detected in human oocytes by RT–PCR. An immunoreactive signal was observed over oocytes using an antibody crossreacting with Smad2 and Smad3, indicating the production of Smad2 protein by the oocytes (Osterlund and Fried, 2000). Smad3 mRNA was detected in mouse granulosa cells (Kano et al., 1999). The mRNAs for Smad2, Smad3 and Smad4 have been detected in the ovaries of postnatal rats and the Smad2 and Smad4 proteins have been immunodetected within the oocytes, the theca and granulosa cells (A. E. Drummond, unpublished). The co-localization of activin-regulated Smads with the activin receptors in oocytes and granulosa cells indicates the presence of a functional activin signalling pathway and supports the hypothesis that activin has paracrine–autocrine roles in the ovary. Finally, mRNAs for Smad 1–7 have been identified in cultured Leydig cells, indicating the presence of a functional pathway in these cells (Goddard et al., 2000).

**Conclusion**

Consistent with the actions of activin, activin signalling components appear to be present in most reproductive tissues. For some tissues, the question of cell-specificity of response to activin can be addressed by examining the sites of receptor and Smad expression. For instance, it is clear that the oocytes and the granulosa cells may be under activin regulation. However, many questions remain unanswered. How can activin have age- and stage-specific effects during folliculogenesis? Which subset of receptors and Smads are involved? Does a switch in the expression of the signalling components explain the various effects of activin? The next challenge will be to obtain a better understanding of the distribution and temporal expression of these activin signalling components and to determine which components are responsible for the specificity of the activin effect. Some studies are now indicating that, under some circumstances, Smad2 and Smad3 are functionally different. Moreover, ALK2 and ALK4 appear to stimulate different pathways (J-F. Ethier, unpublished) and it has been suggested that ALK2 transduces a BMP-like signal. The activation of a particular pathway in preference to any other may explain the differential responsiveness to activin.

The model of activin signalling implies several levels of complexity to permit the differential responses. It is conceivable that the Smad pathway is the core of the activin signalling mechanism but, depending on the cell context, it would have to be modulated by cell-specific intracellular factors. These differentially expressed factors would associate with the activated Smads to induce specific promoters. Unfortunately, as yet, no such intracellular modulators have been associated with any specific action of activin in reproductive tissues. The search for such putative modulators is of great importance to the understanding of how activin modulates the different reproductive processes discussed in this review.

Further studies are needed to determine whether activin A, B and AB (and likewise, inhibin A and B) are functionally similar. The results of such studies will help in the understanding of the significance of the observation that most reproductive tissues exhibit a differential expression of β-subunits at some stage. In addition, it is important that the cellular mechanisms responsible for the specific production of activin and inhibin species are identified.

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