cAMP biological effects possibly on Steroidogenic factor-1 (SF-1) transcriptional activity, which is inhibited by Smad 1 [38]. In contrast, BMP-2, 4 and 6 enhance gonadotropin-induced oestradiol production [34,58]. The same effects, negative on progesterone and positive on oestradiol, have been observed for BMP-4, 6 and 7 using bovine granulosa cells in basal and Insulin-like growth factor-I (IGF-I)-stimulated conditions [35]. In addition, BMP-4 inhibits LH-dependent production of progesterone by granulosa cells from preovulatory follicles (A. Pierre and S. Fabre, unpublished data). Among the different BMP factors tested, only BMP-4 appears to increase ovine granulosa cell proliferation (Fig. 3) [57]. In the rat, BMP-7 represents also a potent stimulator of granulosa cells proliferation [59]. Additionally, BMP-2, 4 and 6 are able to decrease LH-induced androstenedione production by ovine theca cells [58]. Accordingly, BMP-4, 6 and 7 suppress basal and LH-induced androgen production by bovine theca cells [39]. These factors are also potent stimulators of theca cell number and proliferation [39,58].

Steroids are not the only secretion products of follicular cells that are affected by the action of BMPR-1B ligands. Indeed, BMP-2 enhances inhibin-B production in human granulosa-luteal cells [60] and inhibin-A secretion by ovine granulosa cells [34]. Moreover, BMP-4, 6 and 7 have been shown to increase inhibin-A, activin-A and follistatin production by bovine granulosa cells [35].

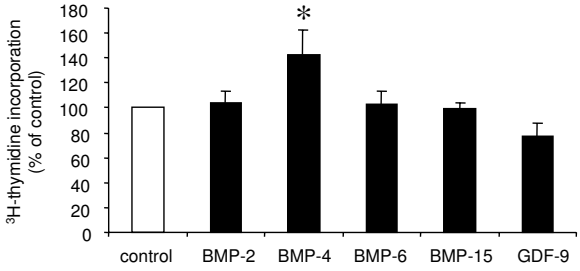

Figure 3
^{3}H-thymidine incorporation into sheep granulosa cells. Granulosa cells from small antral follicles of 1–3 mm in diameter were incubated with ^{3}H-thymidine for 2 h after 48 h of culture in the presence of 3% fetal ovine serum with or without recombinant human BMP-2 (100 ng/ml), BMP-4 (50 ng/ml), BMP-6 (100ng/ml), BMP-15 (200 ng/ml) or rat GDF-9 (1000 ng/ml). Results represent the labeling index (percentage of ^{3}H-thymidine-labelled cells). Data are expressed as percentages (mean ± SEM) of the labeling index of cells cultured in control condition. Asterisk indicates significant difference ($p < 0.05$) compared with control.

The oocyte could be considered as a target cell for BMPR-1B ligands. However, BMP-2 and BMP-4 do not affect oocyte nuclear maturation, cumulus cell expansion, or blastocyst formation following IVF in the bovine species [61].

Collectively, these results indicate that fecundity genes are implicated in mechanisms regulating granulosa and theca cells proliferation and differentiation. Along the folliculogenesis process, *FecX*, *FecG* and *FecB* genes likely control the early steps when follicular growth is closely linked to granulosa cell proliferation. At later stages of follicular development, in antral follicles, *Fec* genes would likely modulate the differentiative effect of FSH, and possibly IGF-I, on follicular cells. Finally, in gonadotropin-dependent large antral follicles, *Fec* genes control follicular cells differentiation and exert a dramatic negative action on FSH and LH-dependent progesterone production. Thereby, they might be implicated in delaying the luteinization process in follicular cells before the time when ovulation and luteinization are triggered by the preovulatory gonadotropin surge.

How do mutations in sheep fecundity genes affect the ovulation rate?

To answer this question, one has to know the functional consequences of the mutations in the normal biological activity of proteins produced by fecundity genes. Obviously, in the case of the *FecX*/BMP-15 gene, $FecX^H$ and $FecX^G$ create STOP codon and then would impair the production of biologically active mature BMP-15. Interestingly, the resulting ovarian phenotype is indistinguishable from the phenotype observed with the other three single mutations $FecX^I$, $FecX^B$ and $FecX^L$, likely enabling the complete peptide production as described for $FecX^I$ and $FecX^B$ [32,62]. Thus, these mutations, as well as $FecX^H$ and $FecX^G$, can be considered as complete "loss of function" mutations for BMP-15. The precise molecular mechanism by which these mutations impair BMP-15 activity is still unclear. It may affect either the formation of BMP-15 homodimers [3] or the efficiency of the processing and secretion of homodimers or their heterodimerization with GDF-9 [32]. The $FecB^B$, Q249R mutation in BMPR-1B, has also been hypothesized as a partial "loss of function" mutation [21,57]. Indeed, using a BMP-specific luciferase reporter in transfected HEK-293 cells, the presence of the Q249R mutation in BMPR-1B is associated with a loss of responsiveness to BMP-4 [57]. This loss in receptor activity is also illustrated by the fact that granulosa cells from homozygous $FecB^B$ carrier ewes are less sensitive to the action of BMP-4 on proliferation and inhibition of progesterone production than those from non-carrier ewes [21,57].