Actin and inhibin are members of the transforming growth factor-β (TGFβ) superfamily of proteins. Actins are protein dimers composed of two β subunits, including activin A (βAβA), activin B (βBβB) and activin AB (βAβB), whereas inhibin is a heterodimer composed of an α subunit in combination with one of the same β subunits to produce inhibin A (αβA) and inhibin B (αβB) (1). Both activin and inhibin were initially isolated from follicular fluid and identified based on their opposing actions on follicle-stimulating hormone (FSH) secretion in pituitary cell cultures: inhibin inhibits whereas activin stimulates FSH release (1). More importantly, activin may be the primary physiological regulator of FSH, as demonstrated in a pituitary perfusion system (2). In this system, activin stimulates FSHβ mRNA 50-fold compared with 3-fold stimulation by gonadotropin-releasing hormone (GnRH) treatment. Interestingly, this dramatic impact was not appreciated when activin was tested in plated cells, presumably because activin accumulation from local gonadotrope production masked the effect of exogenous activin (2). An unrelated glycoprotein hormone, follistatin, has also been isolated from follicular fluid and found to inhibit FSH secretion in an analogous fashion to inhibin. However, studies suggest that follistatin elicits its action solely through binding and neutralizing activin (3).

Systemic infusions of exogenous activin A in non-human primates (4, 5) result in a modest increase in circulating FSH, consistent with a possible endocrine role for activin. Direct studies are not yet possible in the human, however, and indirect models are required to examine the relationship between activin and FSH. The aging human is one such model, and is studied in this issue of European Journal of Endocrinology by Loria et al. (6). A selective increase in FSH secretion occurs across early reproductive aging in females and this increase in FSH occurs more consistently than the increase in luteinizing hormone in males over the age of 50 (7), suggesting a factor other than GnRH, i.e. activin or inhibin, elicits the selective FSH increase. Activin levels have been examined in this model using assays that utilize detergents to separate activin from follistatin and other binding proteins, thus measuring total activin A and not the free or biologically available form (8, 9). Total activin A levels are higher in the midfollicular phase of older compared with younger women of reproductive age (10). However, follistatin in excess of activin (i.e. free follistatin) was detectable at low but similar levels in the two groups suggesting that all circulating activin is bound to follistatin. A larger study found an increase in total activin A (9) across a broad range of ages in males and females. The increase was accompanied by a parallel increase in follistatin (9), a significant portion of which was free follistatin, again suggesting that circulating activin is bound. In this issue, Loria and colleagues demonstrate an increase in total activin A levels across aging in males and an age-specific increase in females, using the largest number of subjects to date (6). They also show that this increase in circulating activin does not correlate with FSH levels. In contrast, the age-related increase in FSH is associated with a decrease in circulating inhibin in males and females (10–16), and inhibin levels correlate inversely with FSH (11, 13). Thus, the indirect model provides evidence that inhibin plays an endocrine role in the control of FSH in the aging human, whereas an endocrine role for activin is not apparent from these studies.

The results of Loria et al. and others are consistent with several lines of evidence which also argue against an endocrine role for activin in the reproductive axis. First, the broad expression pattern of activin β subunits in tissues as diverse as placenta, bone marrow, brain and endothelium (17) is unusual for the classic model of an endocrine hormone. Secondly, follistatin is coexpressed in the majority of activin-producing tissues (18) and binds activin with high affinity and low reversibility under physiological conditions (19) suggesting that tight local regulation results in little biologically available activin in circulating stores. Further, follistatin circulates in molar concentrations in excess of circulating activin as discussed above. Therefore, it appears that the entire circulating pool of activin is bound to follistatin and hence not biologically active under most circumstances. Finally, activin levels are measurable in the greatest quantities in normal humans during the third trimester of pregnancy, a time when circulating FSH levels are suppressed (20). Thus, the circumstantial evidence suggests that the primary role of circulating activin is not endocrine-mediated stimulation of FSH in the human.

Further, the increase in activin A which Loria et al. document across aging does not appear to be related to...
gonadal changes. In females, activin is expressed and secreted by the granulosa cells; however, total activin A levels are similar in premenopausal, postmenopausal (6, 21) and in castrate women (21). In males, activin subunits are expressed in the Sertoli and Leydig cells (22) and one might expect a decrease rather than an increase in activin based on age-related changes. In addition, it is not clear why the increase in circulating activin A levels occurs only in males, with the exception of the slight increase in activin A in women between the ages of 40 and 50 seen in this study (6). One could postulate that testosterone suppresses activin and that the increase in circulating activin is related to the fall in testosterone levels with age (7) or that the fluctuating estradiol levels in the perimenopause are required to stimulate activin, but neither of these hypotheses is satisfying. Since both the $\beta_A$ and $\beta_B$ subunits are found in prostate epithelium (23) it is possible that the increase in circulating activin A results from prostatic hypertrophy in males. It is also possible that a portion of circulating activin may derive from the pituitary and that activin is transiently elevated during the time of greatest fluctuations in FSH levels, such as during the perimenopause. Regardless of the cause for these gender differences in activin levels with aging, the evidence to date leads away from the gonad as the primary source of circulating activin and contributions from other sources must be sought.

Activin $\beta_A$ expression has also been demonstrated in multiple organs including the bone, bone marrow, adrenal, pancreas, pituitary, skin and even in atherosclerotic plaques (24). In addition, activin has been implicated in functions as diverse as inducing erythrocyte differentiation, increasing monocyte migration, stimulating insulin and growth hormone secretion, and enhancing osteoblast proliferation (18). Therefore, the increase in circulating activin across aging likely reflects the sum of changes at the local level in these tissues and may be analogous to the age-related changes in other cytokines such as interferon-\(\alpha\), interleukin-2 and TGF\(\beta\) (25). Activin could then be added to this list of cytokines which have been postulated to play a role in multiple manifestations of aging, from impaired immune function and wound healing to insulin resistance, decreased muscle mass and osteoporosis.

Studies have also demonstrated increased activin levels in patients with renal failure, liver disease and solid tumors (9, 21). Whether activin is responsible for any of the clinical symptoms in these disease states is not clear. However, in transgenic mouse models in which the $\alpha$ subunit of inhibin has been deleted, activin levels are elevated 10-fold and mediate a cachexia syndrome through their action at the activin type II receptor, involving weight loss, anemia, hepatocellular necrosis, lethargy and a decrease in gastric parietal cell number (26). The cachexia syndrome seen in these $\alpha$ inhibin knockout mice may be analogous to cancer-related cachexia syndromes in humans (26). It is possible that the much less dramatic elevations in activin demonstrated by Loria et al. (6) may be responsible for an infinitely milder but similar syndrome in the aging human. However, it seems more likely that the accompanying increase in follistatin demonstrated in some studies (9) would prevent these consequences. Certainly these toxic effects do not occur in the third trimester of pregnancy when activin reaches the highest levels measurable under physiological conditions, possibly due to the accompanying increase in follistatin which renders it inactive (20).

The study by Loria and colleagues (6) provides convincing circumstantial evidence against an endocrine role for activin. It also adds further evidence that gonadally derived activin does not constitute the majority of circulating levels. But the study raises as many questions as it answers. It is clear that follistatin, activin B, and free activin levels must also be evaluated in the same population to assess whether the increase in activin represents biologically available activin and is truly gender specific. It will also be necessary to administer activin directly to humans to analyze its physiological effects. Fortunately, the work in this field is progressing rapidly, and with new assays being developed every day the answers will not be long in coming.

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