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Somatotropins

HISTORICAL DEVELOPMENT

In the early 1930s, it was reported that injections of crude pituitary extracts increased growth rates in growing animals and milk production in lactating animals. Subsequent studies led to purification from pituitary extracts of two peptide hormones—prolactin and "growth hormone" or somatotropin—which are important to growth and lactation. Prolactin has many functions ranging from regulation of limb regeneration and salt balance in amphibians to regulation of mammary growth and function in many mammals. It was named prolactin because it was measured (assayed) on the basis of stimulation of mammary growth in rabbits and rodents. Similarly, the term growth hormone arose from the original assay method which was based on growth promotion. When it became evident that "growth hormone" had many actions in addition to growth promotion, its name was changed to somatotropin. The name prolactin has not been changed to better describe its diverse functions.

Early investigators, working with rodents and rabbits, demonstrated that prolactin was essential to mammary development during pregnancy and to maintenance of lactation. Without replacement therapy with both prolactin and cortisol, lactation in rats without a pituitary (hypophysectomized) is severely depressed and, as a result, their pups lose weight and many die. These observations led to the general view that prolactin was "the" pituitary hormone essential to lactation even though early publications indicated that somatotropin

was active in enhancing milk production in ruminants while prolactin was not. Hormone preparations used during this period were not pure and we knew little of species specificity. This caused considerable confusion regarding apparent interspecific differences. Also, most experiments on lactation were conducted using intact animals where results are more difficult to interpret than those obtained from animals in which confounding effects of endogenous secretions are prevented by removal of appropriate endocrine glands. The critical experiment which established the essentiality of somatotropin for lactation in ruminants was conducted by Cowieer al. (1964). Using hypophysectomized, lactating goats, they found that somatotropin was essential to the maintenance of lactation while prolactin was not.

This and many other studies cited by Hart et al. (1979), and Bauman and McCutcheon (1986) had established by the mid 1960s that somatotropin enhances growth and lactation in farm animals. Application of this knowledge in the animal industry awaited developments in biotechnology required to produce an adequate supply of somatotropin.

CHEMISTRY OF SOMATOTROPINS

Somatotropins are large, complex peptide hormones comprised of 190-199 amino acids. Peptide hormones include insulin, prolactin, somatotropin, luteotrophic hormones and follicle stimulating hormones. These hormones differ from steroid hormones such as estrogen, progesterone and glucocorticoids in a number of important ways. Peptide hormones are proteins with molecular weights ranging from 4 to 22 kg/mole while steroid hormones are small molecules ranging from 0.2 to 0.3 kg/mole. Peptide hormones are not active when administered orally while steroid hormones are. For example, insulin must be injected into diabetics requiring hormone therapy while birth control pills containing estrogen and progesterone can be taken orally. This is because peptide hormones cannot be absorbed until they are degraded to their component amino acids in the digestive tract (as with all proteins) while steroid hormones are small and readily absorbed, unchanged by the digestive tract. Because peptide hormones are highly complex, they and their activities vary greatly across species. Homology among peptide hormones is a measure of similarity in amino acid sequences between two peptides. As homology decreases, the likelihood that a hormone from one species will act in another species decreases. For example, homology between bovine, rat and bovine somatotropins is over 85 percent while homology between human soma-

totropin and bovine somatotropin (BST) is only 70 percent. As a result, BST is active in sheep and rats and completely inactive in supporting growth when injected into humans. Steroid hormones differ from species to species but the differences are small, for example, estrogens from one species or estrogen analogues such as diethylstilbestrol can be expected to be active in all species. A final difference between peptide and steroid hormones is that they differ in their mode of action at the cellular level. Peptide hormones bind to receptors on the cell membrane and exert their action from that site. Steroid hormones enter the cell and are transferred to the nucleus of the cell where they exert their action.
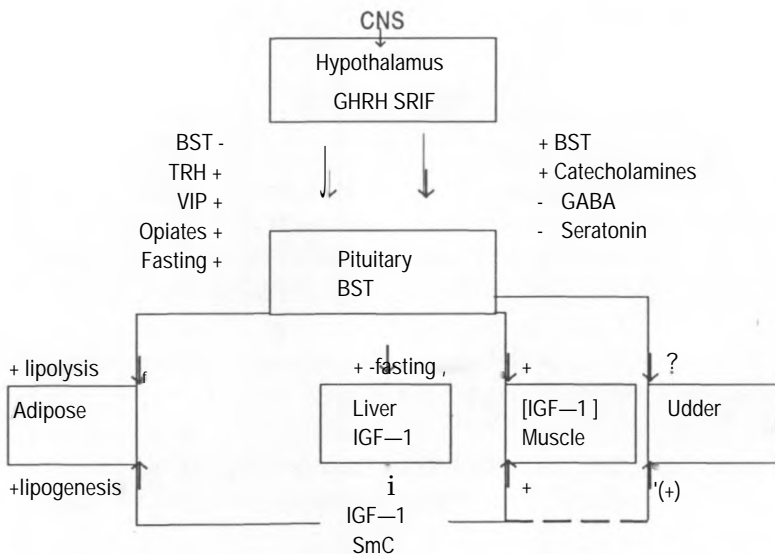
REGULATION OF SOMATOTROPIN SECRETION

The regulation of somatotropin secretion is quite complex as shown in Fig 1. As is true for most pituitary hormones, primary control is dependent upon the balance between a releasing factor (growth hormone releasing hormone [GHRH]) which stimulates secretion and an inhibiting factor (somatostatin or somatotropin release inhibiting factor [SRIF]) which decreases secretion. Growth hormone releasing hormone is a peptide comprised of 48 amino acids and is secreted by the hypothalamus or lower brain. Injection of GHRH increases somatotro-

Figure 1

Diagrammatic representation of the regulation of somatotropin secretion and actions.

pin secretion and, indeed, has been considered as an alternative to administration of somatotropin to enhance growth and milk production. Conversely, formation of antibodies against SRIF, a peptide of 28 amino acids; to reduce SRIF levels results in increased somatotropin release and can enhance growth. This approach has also been considered as an alternative to somatotropin administration. A number of additional peptides, neurotransmitters and other compounds including opiates modify somatotropin release either directly or by modifying GHRH and/or somatostatin secretion or action (Fig 1). Opportunities for modification of somatotropin secretion through manipulation of these "other" factors undoubtedly exist but have not been explored thoroughly.

mechanism (s) of somatotropin action

Administration of somatotropin, specific to a given species, clearly enhances growth rate (ADG) and efficiency (feed/gain) in farm livestock favoring protein over fat accretion at lower feed intakes. It is just as clear that BST administration enhances milk production in dairy cattle. Mechanisms whereby somatotropins produce these responses are not fully understood and, thus, any discussion of mechanism (below) must contain some speculation.

Several mechanisms involved in growth promotion by somatotropin are summarized in Figure 1. It is now clear that a primary action of somatotropin is to enhance the formation and secretion of insulin-like growth factor 1 (IGF-1) by the liver. Insulin-like growth factor 1 is also called somatomedin C (SmC) to indicate that it mediates somatotropin action. Circulating levels of somatotropin do not differ between toy and standard poodles but amounts of IGF1 secreted by the liver do differ causing the differences in size. This illustrates the essential role IGF-1 secretion by the liver in muscle and, probably, acts to increase rates of protein accretion by increasing rates of protein synthesis. The increase in the rate of protein synthesis may be a direct effect on biosynthetic capacity in muscle cells or an indirect effect due to increased satellite cell proliferation leading to increased numbers of nuclei per muscle cell which, in turn, increases biosynthetic capacity.

Until recently, it was considered anomalous that circulating levels of somatotropin become elevated during fasting in many species. The effect somatotropin has upon adipose tissue is to increase capacity for fat mobilization (lipolysis). This was considered consistent with ele-

vated somatotropin, the need for fat mobilization during fasting and reduced fat accretion in fed animals injected with somatotropin. However, IGF—1 stimulates fat synthesis (lipogenesis) and storage. Therefore, if somatotropin increases circulating levels of IGF—1, one would expect the lipogenic effects of IGF—1 to counterbalance the lipolytic effects of somatotropin in adipose tissue. Now, we know that liver cell membrane receptors required for somatotropin binding in liver decrease during fasting, such that the elevated somatotropin levels are not recognized by liver and IGF—1 secretion is not increased. Thus, during fasting somatotropin increases, thereby increasing lipolytic capacity in adipose tissue but IGF—1 secretion by liver and adipose lipogenic capacity are not increased so the net response in adipose tissue is mobilization of fat.

With respect to lactation, the exact mechanism(s) of BST action are not known but some insight is emerging. Three major factors control milk production by the mammary glands: blood nutrient concentrations, blood flow to the udder, and biosynthetic capacity of the udder. Although fatty acids in blood increase slightly when somatotropin is injected into cows in early lactation, changes in blood nutrient concentration due to somatotropin administration are small or absent and certainly not sufficient to explain the increase in milk production reported (Bauman and McCutcheon, 1986). Blood flow to the udder increases in parallel with milk production while arteriovenous differences (uptake) of nutrients from blood remain relatively constant. Thus, it appears logical to conclude that mammary metabolic/biosynthetic capacity is increased by BST treatment resulting in increased product concentrations in venous blood and, in turn, a demand for greater blood flow. Current thoughts are that the effect of BST upon milk production is mediated by IGF-1 and is due, at least in part, to increased numbers of secretory cells, increased biosynthetic capacity per secretory cell or both of these.

REFERENCES

Bauman, D.E. and S.N. McCutcheon. 1986. "The effects of growth hormone and prolactin on metabolism". In Control of Digestion and Metabolism in Ruminants, ed. L.P. Milligan, W.L. Grovum and A. Dobson. Prentiss-Hall, Englewood Cliffs, NJ.

Cowie, A.T., G.S. Knaggs and J.S. Tindal. 1964. "Complete restoration of lactation in the goat after hypophysectomy"./. Endrocrinol. 28:267.

Enright, W.J., L.T. Chapin, W.M. Morely, S.A. Zinn and H.A. Tucker. 1986. "Growth hormone releasing factor stimulates milk production and sustains growth hormone release in Holstein cows". J. Dairy Science, 69:344.

Evock, C.M., T.D. Etherton, C.S. Chungand R E. Evy. 1988. "Pituitary porcine growth hormone (pGH) and a recombinant pGH analog stimulate pig growth performance in a similar matter"./. Anim. Science. 66:1928-1941.

Hart, I.C., J. A. Bines and S.V. Morant. 1979. "Endocrine control of energy metabolism in the cow: correlations of hormones and metabolites in high and low yielding cows for stages of lactation". J. Dairy Science. 62-270.

Nichol, C.S. 1974. "Prolactin physiology". In Handbook of Physiology. Vol. 4, part 2, chap. 32. American Physiological Society. Washington DC.

Reichlin, S. 1986. "Somatostatin: Biosynthesis, regulation of secretion, and role in growth hormone regulation", pp. 405. In Human Growth Hormone, eds. S. Raiti and R.A. Tolman. Plenum Medical Book Company, NY.