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Primary Locus Intervention: A novel approach to treating age-associated hormone insufficiency

There is consensus among practitioners of age-management/longevity medicine that progressive failure of neuroendocrine function leads to hormone insufficiency, which underlies many of the maladaptive consequences of aging. Accordingly, one of the most commonly employed clinical interventions in aging is balanced hormone replacement therapy (HRT). This approach is often quite effective since many of the structural and functional consequence of aging result at least in part from inadequate endogenous hormone supply and/or imbalance of multiple hormone actions upon the body. However, while HRT is effective in opposing many of the more obvious degenerative effects of aging on body composition and function it does little to treat the pathophysiological factors underlying neuroendocrine decline. In fact, HRT may actually accelerate senescence of neuroendocrine elements within the brain and pituitary gland.

Growth hormone replacement therapy (GHRT) which has been the cornerstone of age-management HRT for many years provides a familiar example of this paradox. The basis for prescribing recombinant growth hormone (hGH) to sustain health during aging derived from observation of young adults who received hGH as children to treat short stature. Once those children reached their final height, GHRT was discontinued because hGH was thought necessary only to stimulate growth. However, it soon became apparent that growth hormone deficiency (GHD) in these young adults had significant negative consequences on their health and vitality. Such individuals experienced increased risk for development of life threatening disorders such as high blood pressure, diabetes, cardiovascular disease and cancer. Significant to practitioners of age-management medicine was the fact that these diseases also typically occur in normal adults during middle age and later. Coincidentally, growth hormone production and secretion declines progressively with advancing age, and that such change correlates with increased risk for the same intrinsic diseases observed in GHD young adults. However, it also became apparent in older adults receiving hGH that the hormone had biphasic effects in which overdosing produced many of the same symptoms as deficiency, eg, hyperglycemia, increased blood pressure, etc. These effects were attributed not only to over dosage, but also to the unnatural, pharmacological presentation of the hormone resulting from bolus administration. Because hGH metabolic dynamics is controlled by a feedback network consisting of stimulatory and inhibitory elements, its normal physiological pattern of release from the pituitary is episodic. In contrast, an injection of hundreds of micrograms and even milligrams of hormone produces a "square wave" that not only has the potential for down-stream receptor saturation, but also up-stream distortion of normal feedback relationships. For example, hyper-exposure to GH inhibits transcription of growth hormone releasing hormone (GHRH) mRNA while stimulating that of somatostatin (Bertherat et al 1993). This combined feedback effect causes down-regulation of pituitary GHRH receptors and "disuse atrophy" of the pituitary gland which actually accelerates the age associated decline in its ability to produce hGH (Horikawa et al 1996).

Hypothalamic catecholaminergic and indolaminergic neurons control hGH production and secretion (Blackard and Heidingsfelder 1968) presumably by affecting GHRH and somatostatin neurosecretory neuron activity, respectively. Thus, suppression of

catecholaminergic neuronal activity by negative feedback from exogenous hGH may contribute further to the global cascade of neuroendocrine failure associated with advancing age. Thus, while end-product HRT may be effective in opposing certain aspects of somatic senescence, it fails to simulate youthful endocrine physiology, has a potential for overdosing and may actually accelerate neuroendocrine senescence.

A novel approach to gaining the benefits of HRT without compromising youthful, physiological function within the neuroendocrine system is called PLI therapy. PLI is an acronym for Primary Locus Intervention which is so named because it targets the progressive, age-related decline in hormone production at the highest neuroendocrine level of organization. Unlike end-product HRT, the objective of PLI therapy is to restore feedback and other normal physiological relationships within the brain-neuroendocrine complex and thereby to restore youthful endogenous hormone production/secretion. The intervention is based upon the observation that dopamine receptors decline in the human brain with aging (Wong et al 1997) and the idea that age-distortion of catecholamine (norepinephrine and dopamine) and indoleamine (serotonin) neurotransmitter dynamics is a higher order, if not primary neuroendocrine defect. This concept is supported by the fact that dopamine and norephinephrine are known to promote release of pituitary hormones including GH and gonadotropins (Blackard and Heidingsfelder 1968; Mohandumar et al 1994). During aging, steady state concentrations and turnover of these catecholamines in hypothalamic regions responsible for control of pituitary function are significantly reduced compared to youth while relative concentrations of serotonin increase (Simpkins et al 1977). Presumably, such imbalance leads to inhibitory serotonin dominance These changes may contribute at least in part to the age-related decline in pituitary hGH and other hormones. For example, when catecholaminergic neurotransmission was specifically blocked with drugs, hGH release was reduced. However, this neurotransmitter defect was not irreversible. When catecholamine activity was restored after pharmacological blockade, youthful hGH production and secretion also increased. Catecholamine neurotransmitters were increased by administration of precursors which in turn increased pituitary/serum growth hormone concentrations, restored youthful episodic patterns of secretion (Sonntag et al 1982) promoted its anabolic effects upon the body (Sonntag et al 1985) and extended life (Cotzias et al 1974). Similarly, monoamine oxidase (MAO) inhibitors which reduced catecholamine turnover also improved neuroendocrine function and extended life (Cotzias et al 1974; Ruehl 1997). The fact that these treatments extended life may be attributed to their ability to reduce intrinsic disease, which is known to increase in hormone deficient individuals (such as those suffering GHD or multiple pituitary hormone deficiency). Support for this premise derives from a carcinogenicity research study in which long term administration of a dopaminergic compound significantly reduced seven neoplastic lesions, five nonneoplastic lesions and prevented two age-related, degenerative somatic changes in treated subjects (Walker et al 1998).

Although supporting evidence for PLI therapy has been available for several decades, it has not been widely used in clinical settings because no single product or line of products has yet been created for general application in age-management medicine. This is understandable because the many choices of potentially efficacious compounds make selecting one or another somewhat difficult without specialty training. However, this fact should not create an impenetrable barrier to testing the potential of PLI therapy as a more effective, safer and legal method for treating age-associated hormone deficiency than end-product HRT. Surely physiological rejuvenation of the complete neuroendocrine system would be a better alternative than pharmacological replacement of exogenous hormones. This alternative has actually been available for many years in the form of herbal supplements that are rich in neurotransmitter precursors and monoamine oxidase inhibitors even though they are not restricted by laws governing prescriptions drugs. Some of these compounds include:

- Mucuna pruriens which provides catecholamine and acetylcholine precursors
- Lycium chinense, Uncaria rhynchophylla, and Ginkgo biloba which contains monoamine oxidase inhibitors
- Dimethylaminoethanol which is an acetylcholinesterase inhibitor having the potential to increase brain acetylcholine
- Lepidium meyenii or Maca which directly stimulates production of important pituitary hormones and
- Many other commercially available compounds including somatostatin inhibitory amino acids and antioxidants to support cellular membrane integrity

Since we as practitioners of age-management medicine are constantly seeking new and improved methods for bring better health, vitality and longer life to our clients, perhaps PLI therapy will be a valuable complement to currently employed interventions in aging. I invite your feedback to this suggestion hoping to stimulate interest in developing such new methodologies.

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