An integral view of the neuroendocrine aspects of male sexual dysfunction and aging

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Age is the most important factor associated with sexual dysfunction. The traditional thinking explained this association by the neurovascular events developing with the aging process. More recently, central neuro-endocrine mechanisms resulting from apoptosis in the hypothalamic areas involved in both the production of sex hormones and the control of sexual processes have added a new dimension to human sexuality. This evidence is still controversial but of unquestionable importance in our understanding of endocrine alterations and sexual shortcomings associated with aging.

Key Words: aging, sexual function, hormones

Remembrance

When I first learned of Dr. Klotz's plan to publish an issue of the Journal dedicated to the memory of Dr. Ernest Ramsey, I felt that it represented a rare opportunity to honor and remember an exceptional man and a unique and distinguished urologist. A graduate of Queen's University in Belfast, he completed his urological training at Queen's University in Kingston. He was the first graduate from the recently fully approved program at Queen's in 1971. How much he accomplished in those three decades of academic practice! A surgeon of superior ability, a perspicacious clinician and outstanding teacher, he became a leading figure in Canadian urology. A great deal of what has made our specialty so respected, both nationally and internationally, is in large part due to Ernie's continuous and dynamic determination to follow the path to excellence. His scholarly vision and leadership brought the standards of training to new heights and we, his contemporaries and those who followed, admired and tried to emulate his enthusiasm and remarkable knowledge and skills in all aspects of urology.

But Ernie also possessed unique human qualities outside the profession. Among them, those of a gifted sportsman and musician were those I always admired. Having had the opportunity of being the guest of

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Diane and Ernie on more than one visit to Winnipeg (almost always in winter!) I experienced the grace, warmth and affection of this wonderful couple that exemplified legendary Irish charm and hospitality Figure 1. His absence at informal gatherings and formal meetings such as the Canadian Urological Association is greatly missed. They are just not the same without him. This issue is a fitting memorial to one of the best and brightest. Ernie may have passed on but his influence and contributions to all of us who had the fortune to know him will stay forever.

Ernie had in in-depth knowledge of the hypothalamus-pituitary-gonadal interactions through his life-long interest in prostate health issues. While writing the ruminations below, I felt that he would have enjoyed reading them.

Alvaro Morales

Introduction

The discovery of the effect of vaso-active drugs injected into the corpora cavernosa, over 20 years ago[1] allowed the dynamic study of the penile erection and eventually the description of the physiological processes involved in the mechanisms of tumescence and detumescence. The enormous interest that developed following the initial observations in humans, created a multidisciplinary interest to exploit efficacious forms of treatment aimed at restoring erectile capacity. Since, the research efforts in the area of sexual performance have put a major emphasis on the peripheral (penile) mechanisms. This has translated in the introduction of simpler, safe and effective treatments for erectile dysfunction (ED). The central mechanisms, on the other hand, have not attracted the same degree of interest and are, therefore, less well understood but new research is providing interesting and important indicators for the concept of a fundamental central neuroendocrine integration of several organ/systems responsible for an adequate sexual function. Similarly, ED and alterations in sexual interest can be explained in some instances, by primary damage at one or more settings of their central neuroendocrine control. Epidemiological studies agree that aging is the most relevant contributor to ED. The common view is that such association results from the general deterioration of peripheral neuro-vascular mechanisms as a consequence of chronic conditions (i.e.: diabetes, atherosclerosis) or their treatment (i.e.: anti-hypertensives, hormonal manipulations).

Figure 1. Dr. Ernest Ramsey was President of the CUA for the period 1991-1992. At the Annual Meeting in Winnipeg, to the right, the Ramseys (Diane and Ernie) with the Morales (Diane and Al). Winnipeg, June, 1992.

Evidence of a direct connection from high neuronal centers to the corpus cavernosus of the penis

An important contribution to our understanding of neurological control of a major portion of the sexual response arose from the ability of mapping of central nervous system circuits by transneuronal tracing studies that allows delineation of circuits innervating specific organs. Thus, through a number of elegant experiments using a pseudorabies virus (PRV) capable of trans-synaptic transport and amplification Marson et al., among others,[2] have documented consistent labeling of the following portions of the forebrain within a day of injection of PRV into the penis: the paraventricular nucleus (PVN), medial pre-optic area (MPOA) and supra-optic nucleus (SON). Such findings clearly support the view that these high locations of the central nervous system have a direct genital connection and are of fundamental importance in the control of sexual behavior and function. In addition to the anatomical links, further evidence has been provided, for a direct functional relationship by the induction of penile erections with either electric stimulation or the injection of the dopaminergic agonists apomorphine directly into the MPOA and PVN.[3]

Endocrinology of aging

There is incontrovertible evidence that aging is associated with a progressive decline in the production of several hormones including testosterone, dehydroepiandrosterone, thyroxine, melatonin and growth hormone[4] (anti-diuretic hormone production also declines and may have a role in the nocturia more

commonly associated with bladder outlet obstruction; but this is a matter for another place and time). To what extent the changes in the hormonal milieu contribute to the development and persistence of ED remains speculative. It is known, however, that hypogonadism is associated with a decrease in sexual interest and deterioration in the quality of erectile function. Both of these situations can be improved with androgen supplementation therapy. The therapeutic response has been explained as the result of the central and peripheral activity of androgens. They appear to be fundamental in the signaling leading to the adequate production of nitric oxide (NO) concentrations in the smooth muscle of the penile corpora through the activity of NO synthase.

Could these fields join in an explanation of neuro-endocrine mechanisms?

To integrate the concepts of decreased sexual function and hormonal alterations in the aging male, basic research is providing important information. Until relatively recently, it was believed that testicular function would deteriorate on the basis of decreased gonadal perfusion leading to a loss of Leydig cells population. The causes may be more fundamental and complex than that. Chen and Zirkin[5] postulated as a cause a deterioration of Leydig cells function due to accumulation of free radical damage that could be prevented by placing the Leydig cells in a state of steroidogenesis "hibernation". Wang and her co-workers[6] have shown, in a series of investigations in rodents, that hypothalamic-pituitary functional alterations may not be the only or even the major cause of male gonadal dysfunction. They found evidence of a significant increase in apoptosis in both the hypothalamus and the gonads, a dual alteration that may explain the development of hypogonadism in aging. The areas of the forebrain closely linked to the decrease in GnRh due to this apoptotic process are the same (MPOA and arcuate nucleus) or intimately related to the areas controlling the penile erection process (MPOA and PVN) and the synthesis and release of oxytocin (PVN and supraoptic nucleus). Similarly, peptides normally characterized by their ability to release growth hormone (GH) were found capable of inducing penile erections when injected into the PVN of experimental animals. GH production also declines in relation to advancing age.

Conclusion

Several epidemiological studies have found age to be the most important factor associated with ED.[7] Traditionally, it has been thought that vascular problems frequently associated with advancing age are the most prominent cause of this association. Undoubtedly, there exists an immediate relationship between them. But, other reasons may also play a prominent causal role in the relationship between age and ED. Central neuroendocrine alterations may become fundamental factors to explain the causes of ED and improve on its therapeutic options. Thus, prevention of the progressive apoptotic process in those central neurons closely associated with both hormone production and penile control appears to be a fertile field for research. On a more general view, the role of hormones and their decline in overall men's health is being clarified. Although much controversy still exists, hard evidence is emerging about the unquestionable importance of the integration of those higher centers in some of the manifestations of aging. □

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