

The aging penis: what is it trying to tell us?

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Aging is the price we all pay for living long. While the alternative to aging is a less attractive option, what clinically affect us most during this aging process are the detrimental effects aging has on the smooth muscle throughout our body. Those of us, who have been fortunate enough to enter middle age or better yet, senescence, know how true this is. Consider during this time period the onset of maladies such as essential hypertension, GERD, overactive bladder, farsightedness, constipation, bladder outlet obstruction and the most feared of all aging related symptoms that can afflict any man, erectile dysfunction. All of these conditions have essentially one thing in common—the smooth muscle in that tissue does not function optimally. The main reason for these aging associated dysfunctions is that the smooth muscle mass, at least part of it, within each of these tissues has begun to undergo apoptosis with replenishment by fibrous tissue.

The timing of when this aging related apoptosis of the smooth muscle begins to occur in an individual, specifically in the penis, is assumed to be genetically predetermined. In some men, it can occur in the 3rd to 4th decades of life whereas in others it may not manifest itself until later on in life. It can be extrapolated from data from the Massachusetts male aging study (MMAS) that 20% of men in their 20s have some form of erectile dysfunction and this prevalence increases about 10% per decade such that a 50 year-old man has about a 50% chance of having some problem with his erectile function while a 70 year old will have about a 70% chance (1). The major culprit of this aging related apoptosis seems to be oxidative stress. Oxidative stress is primarily a byproduct of metabolism and since we all “live” by the process of metabolism, oxidation will always win out in the end despite the presence of all the anti-oxidative pathways within the mitochondria and despite all the anti-oxidants that we can throw at the cell. This explains why decreasing caloric intake which essentially decreases metabolism is the only known mechanism that has been shown to increase longevity (2).

However, from experimental studies performed in aging animals, specifically within the corpora of the penis, another previously unrecognized anti-oxidant pathway has recently been identified. This pathway involves the production of nitric oxide (NO) within the cell which, until this NO producing pathway was identified within the smooth muscle cells of the aging corpora (3), NO was only known to be produced in the vascular endothelium, neural tissue, Kupffer cells and the macrophages. NO as a molecule has many functions including being a quencher of reactive oxygen species (ROS) and as such, NO can ameliorate oxidative stress by combining with ROS, for example, to form peroxynitrite. Besides the corpora, this recently recognized NO producing pathway in the corporal tissue is also upregulated during the aging process in a number of other tissues including the peripheral arteries (4).

This begs the question as to how and why NO produced in this specific manner came to be chosen as one of the molecules assigned to such a task as combating oxidative stress. The answer may simply lie in availability. In that time period 1 to 2 billions of years ago when life as we know it today first formed presumably as the result of an increase in oxygen within the atmosphere about a half billion years earlier, there were basically in the atmosphere only three molecules-carbon, oxygen and nitrogen-available for most any task within the cell. These three chemicals obviously offered very few combinations, the most obvious being NO and carbon monoxide (CO). Since the late 1980s, we have become aware of the importance of NO in a multitude of cellular functions including immunity, communication and cell survival. Thus, on the surface, it appears as if NO has been chosen over CO at least by mammalian cells to be involved with most cellular functions other than basic metabolism. That is not to say that cells abandoned CO completely. Although CO in high concentration is known to be toxic to cells, it has recently been discovered that CO

may also possess anti-inflammatory, anti-apoptotic and anti-oxidative effects, and like NO, CO is also known to possess vasodilatory activity (5).

As life evolved and single cells merged to become multicellular organisms, three avenues of NO production, each with its own genetic control and specific translation and transcription, have also evolved. Of these three isoforms of the enzyme, nitric oxide synthase (NOS), that make NO, the one that is primarily committed to fighting for cell survival is the inducible nitric oxide synthase (iNOS) isoform. The gene that regulates this iNOS enzyme is located on chromosome 17 and, as mentioned above, is normally active only in the macrophages and Kupffer cells. iNOS stays inactive in every other cell unless that cell is exposed to specific stimuli that can upregulate its production and NO producing activity. One example of such a stimulus to iNOS is endotoxin. Another appears to be the aging process which is characterized within tissues by apoptosis of the parenchymal cells and an increase in tissue fibrosis. Whether this upregulation of the iNOS gene with aging is simply a response to the increased oxidative stress associated with aging or is the result of some other as yet unknown process associated with aging remains to be determined.

Oxidation, the byproduct of metabolism that causes the smooth muscle cells to undergo apoptosis and fibrosis, will of course impact the function of that smooth muscle. In the penis, this reduced muscle mass may lead to inadequate vasorelaxation of the corporal smooth muscle which in turn does not allow the subtunical veins to be completely compressed against the underside of the tunica albuginea of the corporal bodies. The clinical result is an inability to maintain an erection, so called venous leakage or cavernosal veno-occlusive dysfunction (CVOD). There are some experimental data to suggest that in the human the loss of about 15% of this muscle mass in the penis results in clinical CVOD (6). The earliest sign of this condition occurring in man is the recognized increase in the refractory period that many potent men begin to experience usually sometime around or during their 3rd to 4th decades of life (7).

When evaluated, CVOD turns out to be the most common cause of ED such that up to two-thirds of men who initially present with ED have this as the primary cause of their ED (8). When vascular tests are performed such as dynamic infusion cavernosometry and cavernosography, it is evident that CVOD as a cause of ED is much more prevalent than a pure arteriogenic cause. Today, we categorize patients who have CVOD as having a vasculogenic cause for their ED mainly because the smooth muscle of the cavernosal tissue is embryologically, morphologically and physiologically similar to that of the smooth muscle within the media of the peripheral arterial system and as such this cavernosal tissue

which consists of both the smooth muscle and the cavernosal sinusoids including its endothelium is considered part of the vascular system of the penis. This underlies the statement as to why the penis is considered an outpouching of the peripheral vascular system and indeed, it was this relationship that ultimately led to the hypothesis that whatever causes the peripheral vascular system to dilate-at that time called endothelial derived relaxing factor-must be the same as in the penis. We now know that this erectogenic chemical within the penis is NO that is derived from neuronal NOS (nNOS) and it initiates the series of events that ultimately leads to vasodilatation in the corporal tissue. In the vascular system, the major vasodilator is the endothelial derived NO. Each of these tissues, the endothelium and nerve, has its own isoform of NOS (eNOS and nNOS, respectively), each controlled by its own genome.

If one adheres to the concept that the media of the peripheral arterial system is similar to the smooth muscle within the cavernosa, it makes sense that any systemic disorder that afflicts the cavernosal smooth muscle may also afflict the media of the arterial system or vice versa. With respect to aging, if the cavernosal smooth muscle begins to undergo aging related changes i.e. apoptosis and fibrosis of the trabecular tissue of the cavernosa, it follows that this may also occur within the media of the arterial system (4). When the media of the arterial system undergoes such changes i.e. loss of smooth muscle with an increase in fibrosis, the artery is considered to be arteriosclerotic (not atherosclerotic) and such a process leads to its inability to vasodilate efficiently. Clinically, this arteriosclerosis or stiffness of the peripheral vascular system is the hallmark of hypertension and we have proposed that this aging related change in the peripheral vasculature is most likely the cause of essential hypertension. In fact, based on this observation, our research group believes from a histological point of view that ED is essential hypertension of the penis and, similarly, essential hypertension is ED of the peripheral vascular system. Clinical data to support this assumption that ED and essential hypertension is the same disease albeit in two different tissues may be gleaned from the results of both the National High Blood Pressure Education Program and the MMAS where the aging related prevalence of hypertension in men (9) appears to be exactly the same as the prevalence of ED as reported in the MMAS (1).

The recognition that NO is a potent quencher of reactive oxygen species and that iNOS is upregulated in the cavernosa of the aging penis suggested to us that we may be able to take advantage of this observation to curb the negative effects of aging i.e. smooth muscle loss and increase in fibrosis within the cavernosal tissue. In other words, could we delay or even prevent the onset of aging related CVOD? Since the PDE5

inhibitors are known to upregulate the effects of NO by inhibiting the degradation of its second messenger, cGMP, we initially tested this hypothesis in aged animals and found that continuous PDE5 inhibition, presumably enhancing the upregulation and function of iNOS, not only prevented or delayed the onset of aging related apoptosis and fibrosis, but even suggested that this treatment may simultaneously increase SMC production within the penis (10). Further evidence to support this anti-apoptotic and anti-fibrotic role of the PDE5 inhibitors can be gleaned from the study of Schwartz *et al.* where chronic PDE5 inhibitor treatment to men undergoing radical prostatectomy demonstrated that the PDE5 inhibitor therapy not only prevented the loss of smooth muscle within the cavernosa but, as in our animal model, tended in some patients to increase the amount of smooth muscle within the cavernosa (11). This anti-fibrotic effect of the PDE5 inhibitors has also been extended to patients who have had prolonged periods of priapism where chronic treatment with these PDE5 inhibitors seem, at least observationally, to minimize the known fibrosis and scarring within the cavernosa that occurs after prolonged priapism (12).

In conclusion, it was the aging penis in the early 1990s that bore witness to one of the major discoveries in urology i.e. the role of the NO molecule in the erectile response (13). Today, two decades later, again via another cellular pathway for synthesizing NO, the aging penis is now providing us with evidence of how the body attempts to fight the aging process. The recognition that chronic treatment with drugs that upregulate the effects of NO from this iNOS pathway may have a beneficial effect on either slowing or reversing the aging changes within the penis has opened up new avenues of investigation to try to possibly halt, prevent or delay the onset of ED. Since it appears that what occurs within the aging penis does not stay within the aging penis, it is our belief that the aging penis will continue to provide us with insight into how we may be able to prevent or delay the onset or progression of other aging related maladies such as essential hypertension, congestive heart failure, overactive bladder, certain forms of bladder outlet obstruction and other aging related muscular dysfunctions.

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None.

Footnote

Conflicts of Interest: The author is a co-recipient of a patent assigned to LA Biomed at Harbor-UCLA Medical Center on the use of PDE inhibitors to prevent fibrosis.

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