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Understanding the Pathophysiology of the Overactive Bladder in Elderly through the Study of a Specific Muscle Blocker on the Bladder Contractions

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Overactive Bladder Syndrome (OAB) is a condition that affects a large proportion of the population. Its symptoms of urgency, urgency-incontinence, and nocturia associated with increased urinary frequency are closely related to a decline in physical well-being and individuals' psychosocial integration [1-3]. It is known that patients with OAB have an increased risk to develop depression and other psychological disorders [4,5]. Among its various etiologies, bladder outlet obstruction is a major cause in men over sixty years of age. This group of men has varying degrees of obstruction secondary to benign prostatic hyperplasia (BPH) and OAB is a very important problem among them. Besides of that, the pathophysiology of OAB has not been well explained [4,6,7]. Efforts have been made in recent years to clarify the mechanisms involved in the development of this condition and to better understand the pathophysiology process, which can be the key to the development of new treatment methods and prevention.

Studies with endothelial cells subjected to energy deprivation by inhibiting glycolytic pathway, demonstrated that under situations of cellular stress (such as aging and benign prostatic hyperplasia), there is a rapid increase in concentrations of intracellular calcium, mediated through IP3. It is known that the same phenomenon is observed in other situations of ischemia or hypoxia. Schaffer et al. demonstrated that this rapid increase in the cytoplasmic calcium concentration could be blocked by Xestospongin C [8], which points out the importance of receptor of inositol 1,4,5 triphosphate (IP3) in cellular adverse situations. These data lead us to believe that the smooth muscle cells of the bladder, under a situation of chronic ischemia and reperfusion, acidosis and free radicals, may be constantly subjected to a regime of the raise of intracellular calcium concentration and consequently greater contractile excitability. These phenomena could explain the appearance of detrusor overactivity in situations of partial bladder outlet obstruction.

Understanding the importance of IP3 in the physiology of the contraction of smooth muscles, the existence of a selective blocker at the receptor level is of great value in order to study the intracellular signaling mechanisms that trigger muscle contraction in details.

Xestospongin C is a natural product isolated from marine sponges of the Pacific Ocean. Studies demontrated that the Xestospongin C inhibits the release of Ca^{2+} induced by IP3 blocking calcium channels pores and the calcium pump of the sarcoplasmic reticulum, inhibiting the cascade of muscle contraction [9,10]. Xestospongin´s structure has a liposoluble core with two nitrogen units linked. Its structure appears to be spatially complemented to the pores of IP3 receptors, to the calcium voltage dependent channels and to the potassium dependent voltage channels [11].

Based on the background from the literature we developed an experiment which involved the use of in vitro blocker IP3 - Xestospongin C (Sigma, S Louis MO), with the objective to determinate the direct action of this substance inhibiting the contraction of the muscle fiber, under different electrical and pharmacological stimuli. During the experiment detrusor strips were extracted from the bladder dome of 15 elderly male guinea pigs (24 months old). Detrusor contractility was evaluated through electrical field stimulation and through exposures to solutions of carbachol (10uM/l), ATP (10uM/l) and KCl (80uM/l). After Xestospongin C, amplitude of muscle fiber´s contractions decreased 82% under the EFS ($p<0,01$), 86% ($p<0,01$) under carbachol stimulation; 19% ($p<0,01$) under the ATP stimulation; and 66,7% ($p<0,01$) under KCl stimulation. Through this research, we showed that Xestospongin C is capable of efficiently inhibit the phasic detrusor contractions in vitro, enabling the development of an appropriate voiding contraction. The interstitial cells or the smooth muscle and its clinical applicability and mechanism of action still need to be studied in future researches. Therefore, we conclude that blockade of this pathway at the IP3 receptor is an effective method of inhibiting the detrusor contraction and these findings may sign for the development of new substances or therapeutic targets, allowing a better control of the symptoms and better understanding of the OAB pathophysiology.

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