CHAPTER 17

INTERCELLULAR COMMUNICATION AND BLADDER FUNCTION

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BACKGROUND AND INTRODUCTION

Urinary incontinence resulting from abnormal bladder function is an extremely common problem affecting millions of men and women around the globe. Many diseases, such as stroke, diabetes mellitus, and benign prostatic hyperplasia (BPH), as well as the ravages of advancing age, contribute to altered bladder function. While urinary incontinence is clearly a multifactorial disease, one prevalent manifestation, known as urge incontinence, is related to uncontrolled and involuntary bladder contractions (i.e., bladder overactivity). This overactivity is the result of increased detrusor smooth muscle contractions. The precise physiological mechanisms contributing to the overactive bladder are not clearly understood. However, two different hypotheses, myogenic and neurogenic, have been advanced. The extant clinical and laboratory data support both hypotheses, but this report will focus exclusively on myogenic considerations. However, it should be emphasized that regardless of the precise etiologic cause of bladder hyperactivity, the physiological impact is the same; detrusor myocytes contract spontaneously, causing urinary incontinence.
ELECTROPHYSIOLOGICAL PROPERTIES OF DETRUSOR MYOCYTES

The electrophysiological properties of detrusor myocytes have been extensively studied, using patch clamp techniques, in cultured and freshly isolated cells in various animal and human tissues. Although the majority of studies have not been performed on rat detrusor myocytes, there is a growing experimental literature that suggests that altered electrical properties of nonjunctional ion channels (K⁺, Ca²⁺, etc.) on the detrusor myocytes are involved in the etiology of urge incontinence and bladder hyperactivity. While such studies provide valuable insight into the excitability of individual bladder myocytes, they do not provide a complete description of how such signals are integrated into a coordinated tissue response. Therefore, in an attempt to provide further mechanistic insight into the etiology of bladder hyperactivity, we have begun to investigate the role of intercellular communication through gap junctions in the bladder smooth muscle from normal and obstructed rats. Undoubtedly, knowledge of the whole tissue electrical properties of detrusor smooth muscle is an absolute prerequisite to understanding the syncytial behavior of the bladder.

CHARACTERISTICS OF CONNEXIN43-DERIVED GAP JUNCTION CHANNELS

Gap junctions are membrane specializations comprised of individual aqueous channels that mediate the intercellular movement of ions, and second messenger molecules and metabolites with molecular weights up to ≈1000 daltons. Each individual gap junction channel represents a dodecahedral structure formed by the union across the extracellular space of two hemi-channels or connexons, one derived from each cell of a pair. Each hemi-channel is in turn formed by six homologous membrane-spanning proteins called connexins (Fig. 1). The connexins form a gene family, with more than a dozen mammalian connexins types thus far identified. The connexin gene products are named according to their predicted molecular weights, which range from 26 to 56 kd. However, despite the variety of known gap junction proteins, connexin 43 (Cx43) is one of the most predominant and physiologically relevant connexins expressed in smooth muscle. Recent studies have identified mRNA for Cx43 in both rat and human detrusor myocytes. Unless otherwise stated, this report focuses exclusively on a discussion of the contribution(s) of Cx43-derived gap junction channels to bladder physiology and function.