THE ROLE OF RHO-KINASE (ROK) in regulation of smooth muscle contraction has been an exciting area of investigation for reasons spanning interests in defining cellular signaling systems to insights into potential (and actual) therapies designed to treat smooth muscle contractile disorders. Smooth muscle contraction ultimately requires actomyosin cross-bridge activation, and the regulation of smooth muscle contraction can be described by a complex signalosome consisting of signaling pathways that are involved in tension transmission from the cytoskeleton to the extracellular matrix (5a). Entry of myosin into the cross-bridge cycle requires myosin light chain phosphorylation (2), which is regulated primarily but not entirely by Ca$^{2+}$-dependent myosin light chain kinase (5). A generally accepted mechanism for ROK action is phosphorylation of the myosin-targeting subunit of myosin light chain phosphatase, MYPT1, resulting in inhibition of myosin light chain phosphatase. Such activity increases the degree of myosin phosphorylation and, therefore, contractile tension. Thus, when a contractile stimulus both increases Ca$^{2+}$ entry and activates ROK, a stronger contraction will occur than when a contractile stimulus causes an increase in Ca$^{2+}$ entry alone (i.e., ROK causes Ca$^{2+}$ sensitization). ROK may regulate actin polymerization via LIM kinase (11) and heat shock protein 27 (4).

Spurred on by provocative and clinically relevant findings such as dilation of human coronary arteries by ROK inhibitors, the field has moved rapidly forward, and there are indications that ROK inhibitory therapy may provide relief to patients with disorders involving such diverse smooth muscle contractile dysfunctions as hypertension, vasospasm, stroke, asthma, bladder overactivity, and erectile dysfunction (9, 10, 15–18). On the basis of this momentum, one might reasonably conclude that ROK inhibitors would be expected to cause relaxation of all smooth muscle types by causing reductions in MYPT1 phosphorylation and actin polymerization. The study by Walsh et al. (20) in this issue suggests otherwise and provides more than one reason for investigators interested in understanding the vast complexity of the smooth muscle contractile signalosome to refrain from closing the book on the ROK story.

During the urine storage phase of the bladder, urethral circular smooth muscle appears to play a critical role in ensuring bladder continence (1, 8, 22), and precisely how urethral smooth muscle contraction is regulated is of considerable interest. Walsh et al. (20) present data showing that rabbit urethral smooth muscle displays a non-zero basal myosin phosphorylation level. That is, when “at rest” (i.e., not stimulated to contract by addition of a contractile stimulus), actomyosin cross bridges are “on” to some degree. Qualitatively, this is not different from what is seen in other smooth muscles. For example, vascular, tracheal, and bladder smooth muscles display basal myosin phosphorylation levels of between ~15 and 35% (3, 7, 14). In rabbit bladder, this basal level is sensitive to muscle length; stretching bladder strips from slack length to the optimum length for contraction decreases myosin phosphorylation from ~25 to ~15% (13). Moreover, basal myosin phosphorylation is greater in the bladder dome than in the midbody (7, 13). In pig carotid, rabbit bladder and rat anococcygeus smooth muscles, myosin phosphorylation must be increased to ~15% before contraction occurs (14). Why this is so remains a mystery, but it could be due to cooperative cross-bridge attachment, thin filament regulation, or some other mechanism.

What is dramatic about the finding of Walsh et al. (20) is the very high basal myosin phosphorylation level reported for rabbit urethra and the impressive species differences identified when comparing myosin phosphorylation levels. In rabbit urethra, basal myosin phosphorylation is over 65%, whereas in the rat urethra, basal myosin phosphorylation is more in line with that found in other smooth muscles. This confirms that smooth muscle motor proteins are, at the very least, “idling” at rest. Most studies of smooth muscle focus on mechanisms involved in regulating stimulus-induced increases above the basal level in myosin phosphorylation. The study by Walsh et al. (20) suggests that equal effort should be applied to understanding mechanisms regulating “resting” tissue levels of myosin phosphorylation. Moreover, although considerable effort has been exerted in early and recent studies on the methodology by which smooth muscle enzymes responsible for regulating myosin phosphorylation are “stopped” during physiological experiments (see Refs. 3 and 19, for example), the study by Walsh et al. (20) revisits this technique and provides provocative rationale for reexamination of the optimum “quick-freeze” method. Given the importance of myosin phosphorylation in regulation of contraction, this should be of considerable interest to all smooth muscle biologists.

Perhaps the most intriguing finding by Walsh et al. (20) are the data showing that whereas ROK inhibitors effectively inhibit rabbit urethral contractions, they do not reduce myosin phosphorylation, nor do they appear to affect actin polymerization status. The mechanistic door is left open. Physiological investigations generally seek to clarify the workings of complex systems, and in this electronic and genomic age, it is tempting to settle quickly on general models, ignore lose ends and species variations, and move on. However, the best science forces us to reevaluate and reconsider comfortable paradigms. Only in this way can we ensure that the ultimate model of a complex system is the most accurate one. In this context, the article by Walsh et al. (20) is worth a full read.

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Editorial Focus

DISCLOSURES

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REFERENCES


