

## **ABSTRACT**

**Demonstration of an attenuating role for cyclic guanosine monophosphate (cGMP) in the regulation of contractile tension in the guinea pig tracheal smooth muscle.**

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Modulators of guanylate cyclase activity and cGMP level were used in this study to demonstrate the presence and importance of activation of this system in the guinea pig tracheal muscle. On resting muscle tension, the modulators sodium nitroprusside, zaprinast and 8-bromo-cGMP were used to increase and to mimic the levels of cGMP respectively, consequently they inhibited the resting muscle tension. Alternatively, when the modulators methylene blue and cystamine were used to decrease cGMP levels, the resting muscle tension increased. Together, these results suggest the presence of cGMP and an attenuating effect on tension in the tracheal muscle. This attenuating effect of cGMP was not a significant component of the relaxation phase of the biphasic response elicited by in vitro electrical field stimulation of guinea pig tracheal smooth muscle. This suggestion is based on the results with methylene blue and cystamine which only reduced the duration of the relaxation but produced no significant change in the magnitude of the other parameters. Zaprinast also did not produce any significant change in the

relaxation phase of the biphasic response which was neural in origin and similar to the NANC response.

Contractile tension was also not the triggering mechanism for the cGMP attenuating effect in the tracheal muscle, although the results with zaprinast and cystamine suggest that cGMP attenuated histamine-induced contractions of the tracheal muscle when it was subjected to sustained stretch of 1.0g tension. In fact, the attenuating effect of cGMP was progressively reduced as the contractile tension was increased with various doses of histamine and thus ruling out contractile tension as a triggering mechanism for cGMP release.

There was, however, evidence which links the cGMP attenuating effect to the magnitude of sustained stretching tension placed on the tracheal muscle. For example, sustained stretching tension on the tracheal muscle potentiated histamine-induced contractile tension, but in the presence of cystamine (12.0 $\mu$ g/ml) the magnitude of potentiation was greater, and this was further increased from 33% to 45% when the sustained stretching tension on the muscle was increased from 1.0g to 2.0g in the presence of 1.2 $\mu$ g/ml histamine. Under similar conditions, cystamine also increased the potentiation of histamine-induced contraction from 23% to 31% when the sustained stretching tension on the muscle was increased from 1.0g to 2.0g in the presence of 6.0 $\mu$ g/ml histamine. Additionally, when histamine-induced contractions were produced under a larger

range of sustained stretching tensions, the magnitude of potentiation was maximal at a stretching tension of 2.0g, but in the presence of zaprinast (12.0 $\mu$ g/ml), the magnitudes of contractions produced by single doses of histamine (1.2 $\mu$ g/ml and 6.0 $\mu$ g/ml) were increasingly inhibited over the entire range of sustained stretching tension (0.5g to 4.0g) including the tension at which the potentiating effect was maximal. Moreover, the magnitude of zaprinast-induced inhibition was dependent on the magnitude of stretching tension placed on the tracheal muscle. This inhibitory effect on contractile tension, triggered by sustained stretching tension placed on the tracheal muscle, could not be attributed to disruption of the organisation of the contractile elements of the muscle. In fact, the results suggest the presence of a guanylate cyclase/cGMP system in the tracheal muscle. This system seemed to function as a cGMP-mediated retarding mechanism on the magnitude of contractile potentiation which is triggered concurrently by sustained stretching tension placed on the guinea pig tracheal muscle.