Can inorganic ions be used to modulate tone in sheep isolated internal anal sphincter?

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Progressive weakening of the anal sphincter complex with age, is a common cause of faecal incontinence (FI). In man, α₁-adrenoceptor agonists such as phenylephrine (PE) and L-erythromethoxamine (LEM) have been shown to increase sphincter pressure in FI patients although not without side effects (Cheetham, Kamm and Phillips, 2001; Nisar et al., 2007). The aim of our study was to investigate (i) whether sodium orthovanadate (SOV) can increase tone in a sheep isolated internal anal sphincter (SIAS) model by inhibition of tyrosine phosphatase and (ii) whether lithium ions can modulate responses to α₁-adrenoceptor agonists by inhibiting the recycling of intracellular signalling molecules (IP₃).

Using a similar method to Mundey et al. (2000), SIAS strips that had generated spontaneous myogenic tone were used to construct cumulative contraction curves to SOV or α₁-adrenoceptor agonists. Both the magnitude and duration of responses to the α₁-adrenoceptor agonists PE and LEM were compared in the presence and absence of lithium ions. To measure the duration of the response to α₁-adrenoceptor agonist, measurements were taken at 5 minute intervals for a total of 60 minutes after administration of the final dose (which was designated as time 0).

SOV, but not lithium, caused a concentration-dependent contraction of SIAS muscle strips (pEC₅₀ 3.48 ± 0.12; n=8). The maximal response to SOV did not differ significantly from that observed with α₁-adrenoceptor agonists using a one-way ANOVA with Bonferroni post-test (Rₘₐₓ SOV 140 ± 28% of basal tone, n=8; Rₘₐₓ PE 129 ± 37%, n=6; LEM 85 ± 27%, n=6). Based on paired t-tests, the presence of 1mM lithium chloride did not significantly affect the pEC₅₀ or maximal responses to either PE or LEM. Under control conditions, responses to both agonists declined over the 60 minute period: the responses reduced to 56 ± 13% (PE; n=6) and -20 ± 14% (LEM; n=8) of the response at time 0 respectively. Based on unpaired t-tests, the presence of 1mM LiCl significantly attenuated the reduction in tone observed with agonists within 15 minutes. And, at 60 minutes responses in the presence of lithium were 123 ± 8% (PE; n=7; p=0.0007) and 62 ± 8% (LEM; n=8; p=0.0002) of the response at time 0. Similar observations were made in the presence of 0.5mM lithium sulphate but not 1mM rubidium chloride.

This work demonstrates that, in a SIAS model, inorganic ions can be used to influence sphincter tone either alone, as in the case of SOV, or to enhance the duration of responses to α₁-adrenoceptor agonists.

