A COMPARISON OF THE EFFECT OF SNP AND UK-114,542, A PDE5 INHIBITOR, ON SHEEP ISOLATED INTERNAL ANAL SPHINCTER MYOGENIC TONE: DIFFERENTIAL EFFECT OF L-NAME AND ODQ

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Neurogenic release of nitric oxide (NO) causes relaxation of sheep internal anal sphincter (IAS) myogenic tone (Mundey *et al*., 2000). L-NAME and ODQ, an inhibitor of soluble guanylyl cyclase (sGC, Celleck *et al*.,1996), blocked these responses and increased tone *per se*. These findings suggest that at rest basal release of NO suppresses myogenic tone. The NO/cGMP (guanosine cyclic monophosphate) pathway relaxes smooth muscle, with cGMP levels governed by the rate of synthesis by sGC and the rate of degradation by a cGMP-specific phosphodiesterase (PDE5) (Carvajal *et al*., 2000). We have compared the effect of sodium nitroprusside (SNP) and UK-114,542, a selective inhibitor of PDE5 (Ling *et al*., 2000), on myogenic tone in the absence and presence of L-NAME and ODQ.

Individual strips (10x2x2 mm) of the sheep distal internal anal sphincter were secured to a perspex holder and incubated in 20ml isolated organ baths containing Krebs-Henseleit solution (pH 7.4) gassed (95% O_2 /5% CO_2) at 37 °C. An initial 2g of tension was applied and the tissue was allowed to equilibrate and develop myogenic tone for 30–40 min (Mundey *et al*., 2000). SNP and UK-114,542 were added cumulatively at 10 min intervals.

The mean myogenic tone of the preparations used was 3.63 ± 0.23g (n=59). UK-114,542 (log EC_{50} -7.27±0.09, n=11) was approximately 5-fold more potent than SNP (log EC_{50} = -6.43±0.12, n=8) in causing a concentration-dependent inhibition of myogenic tone. At maximally-effective concentrations, both agents caused greater than 90% inhibition of myogenic tone. In the presence of a submaximal concentration of UK-114,542 (30nM), the potency of SNP was significantly increased 5-fold from log EC_{50} - 6.31±0.06 to -7.08±0.13 (n=8).

Table 1. The effect of L-NAME (100μM) and ODQ (3μM) on the -log EC_{50} values for SNP and UK-114,542 in the sheep anal sphincter.

	Control	L-NAME	Control	ODQ
SNP	6.50±0.13	6.43±0.11	6.16±0.07	4.63±0.24*
UK-114,542	7.20±0.10	6.92±0.20*	7.67±0.07	7.59±0.10

The values shown are the mean ± sem of 7-14 observations. * - denotes a statistically significant difference from control values (paired Student t-test $p<0.001$).

Table 1 shows that L-NAME (100μM) reduced the potency of UK-114,542 by approximately 2-fold, without affecting the response to SNP. In marked contrast, 3μM ODQ reduced the potency of SNP by 30-fold, but failed to affect UK-114,542-induced relaxations.

These data indicate UK-114,542, a selective inhibitor of PDE 5 (Ling *et al*., 2000), causes potent inhibition of myogenic tone in the sheep anal sphincter. This observation, coupled with its ability of low concentrations to enhance SNP-induced relaxations, is consistent with a significant role for basal nitric oxide and PDE 5 in regulating myogenic tone. However, the finding that L-NAME produced only modest inhibition of responses, while ODQ was inactive, suggests that a major part of its action is independent of basal release of nitric oxide and generation of cyclic GMP. Further studies are warranted to establish whether the differential effect of ODQ and L-NAME on UK-114,542 is observed in other smooth muscle preparations.

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