J. Pharm. Pharmacol. 1998, 50 (Supplement): 203

Role of cyclic nucleotides in oestrogen-induced vascular relaxation

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Epidemiological studies show that oestrogens have protective cardiovascular actions in pre-menopausal women and post-menopausal women receiving Hormone Replacement Therapy (Henderson & Paganini-Hill, 1991). Such protection may be related to the dilator actions of oestrogens but the mechanism is unclear. Oestrogen-induced dilation has been suggested to involve protein kinase C inhibition (Magness *et al*, 1989) or increases in cyclic nucleotides (Mugge *et al*, 1993) or inhibition of Ca influx. The latter was considered most likely to account for oestrogen-induced relaxation of rat portal vein (Al-Hawadi & McCurrie, 1997). In the present experiments we compared relaxant effects of 17ß oestradiol (EST) with those of agents which increase cyclic nucleotide concentration: isoprenaline (ISOP) and theophylline (TH) which raise cAMP and guanosine (G), guanosine triphosphate (GTP) and sodium nitroprusside (SNP) which increase cGMP.

Portal veins from male Hooded Lister rats (200-320g) were set up in Krebs' solution containing 10μM indomethacin under 0.5g tension (37°C, 95% CO_2, 5% CO_2). A control concentration-response curve (CRC) to KCl (2-128mM) or $PGF_{2\alpha}$ (PGF, 2-200μM) was constructed and repeated after incubation with EST (2-8μM) or vehicle (60% ethanol/ 40% water) or ISOP (1-10μM), TH (1-10μM), G (100μM), GTP (200μM) or SNP (1-10μM) for 20 minutes. No vehicle effects were seen.

EST caused concentration-related reduction in contraction to both agonists. EST (8μM) reduced the maximal response (E_{max}) to KCl and PGF to 50.5±8.0 and 73.1±4.7% respectively, displacing CRCs to the right. ISOP (1-10μM) caused little change in responses to KCl or PGF, TH (10μM) which raises cAMP by inhibiting phosphodiesterases, slightly decreased PGF E_{max}.

Relaxation was generally greater when cellular cGMP rather than cAMP was increased. G (100μM) and GTP (200μM) caused small rightward shifts in PGF CRCs with no change in E_{max}. SNP (1μM) shifted the KCl curve to the right and reduced E_{max}; similar, smaller changes occurred with SNP (10μM) when PGF was the contractile agent. Methylene blue (MB, 10μM), which inhibits guanylate cyclase and decreases cGMP, partly reversed effects of SNP on KCl concentration response curves. MB similarly affected actions of SNP on PGF concentration-response curves. However, MB (10μM) caused little change in oestrogen-induced relaxation of contraction induced by either constrictor; no change in E_{max} was observed (Table 1).

Table 1. Comparison of relaxation (% reduction in E_{max}) of responses to KCl (64mM) or $PGF_{2\alpha}$ (100μM) by 17ß oestradiol (EST, 8 μM) or sodium nitroprusside (SNP, 1-10μM) in the absence or presence of methylene blue (MB, 10μ M). n = 4-6. *Significantly different from SNP alone, P<0.05, paired t-test.

RELAXANT	CONTRACTILE AGENT	
	KCl	$PGF_{2\alpha}$
EST	49.5 ± 8.0	26.9 ± 4.7
EST + MB	53.9 ± 10.1	28.3 ± 2.6
SNP (1μM)	24.1 ± 7.7	-
SNP + MB	10.3 ± 4.3*	-
SNP (10μM)	-	30.1 ± 4.8
SNP + MB	-	19.9 ● 3.6*

In these experiments EST caused substantial decreases in magnitude of contraction elicited by both KCl and PGF while the effects of increasing cGMP or cAMP were inconsistent and qualitatively different from those of oestrogen. We conclude that, while changes in cyclic nucleotides may accompany oestrogen actions, such changes do not adequately account for the oestrogen-induced relaxations observed.

Al-Hawadi, AH, McCurrie, JR, (1997) *J Pharm Pharmac*, **49**, S4, 111.

Henderson, B & Paganini Hill, A (1991) *Arch Intern Med*, **151**, 75-78.

Magness, RR & Rosenfeld, CR (1989), *Am J Physiol*, **256**, E536-42.

Mugge, A *et al* (1993), *Cardiovasc Res*, **27**, 1939-42.