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Effects of tamoxifen on contractile responses of rat aorta

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Tamoxifen, an oestrogen antagonist with partial agonist activity used to treat breast cancer, is reported to reduce the risk of myocardial infarction (McDonald et al, 1995). The latter may be related to the partial agonist activity and could involve general vasodilation which appears important for cardiovascular protection by oestrogens during Hormone Replacement Therapy (Rosano et al, 1993). Since tamoxifen inhibits protein kinase C *in vitro* and relaxes vascular muscle (Babaei *et al*, 1997), we compared acute and chronic effects of tamoxifen on contraction of rat aorta induced by phorbol dibutyrate (PDB) a potent, specific activator of protein kinase C (PKC) and by the vasoconstrictor, $PGF_{2\alpha}$ (PGF).

Aortic rings were prepared from 3 groups of Hooded Lister rats (200-320g). Group 1 (male, no pretreatment) were sacrificed by cervical dislocation. Aortic rings set up in Krebs' solution containing 10μM indomethacin under 2g tension (37°C, 95% O_2 , 5% CO_2) were contracted with PGF (10μM) or PDB (2nM), approximately EC_{80} concentrations giving responses of 1.50±0.9g and 1.58±0.28g respectively (n = 28). When contraction was stable, 17ß oestradiol (EST, 1-20μM) or tamoxifen (TAM, 1-20μM) was applied for 40 mins; only 1 agent was used in each tissue. Preliminary tests showed no difference in oestrogen-induced relaxation between male and female rats (Babaei, 1998). Like EST, TAM caused concentration-related relaxation, expressed as % reversal of contraction; relaxation of PDB-induced contraction being considerably greater (Table 1).

Table 1. Relaxation of contraction (%) induced by $PGF_{2\alpha}$ (10μM) or PDB (2nM)

Relaxant	$PGF_{2\alpha}$	(n)	PDB	(n)
EST (20μM)	56.7±3.5	(11)	100	(16)
TAM (20μM)	30.7±9.2	(7)	51.9±5.7	(4)

Effects of tamoxifen pretreatment on contractile activity were studied in two groups of female rats following oral treatment with TAM, 0.3 or 0.5mg/kg/day or vehicle (2% methylcellulose). Group 2 were treated for 5 days; Group 3 for 10 days (n = 4-7). Following sacrifice by a lethal dose of sodium pentobarbital (200mg/kg, IP), aortic rings were set up as described above. Contractile responses of aortae from tamoxifen-treated animals to PGF (10μM) or PDB (2nM) are shown in Table 2.

Table 2. Contractile responses expressed as mean ±SEM (g) of aortic rings to $PGF_{2\alpha}$ (10μM) or PDB (2nM) following tamoxifen pretreatment for 5 or 10 days (n =4-7). Significantly different from control, *P<0.05, **P<0.01 (unpaired t-test)

Treatment	TAMOXIFEN mg/kg/day		CONTROL 2% methylcellulose	
Response to:	PGF	PDB	PGF	PDB
5 days				
0.3mg/kg	1.18±0.08	0.63±0.17	1.02±0.09	0.88± 0.2
0.5mg/kg	1.13±0.16	0.82±0.16		
10 days				
0.3mg/kg	1.02±0.08	0.37±0.18**	1.13±0.08	0.97±0.09
0.5mg/kg	1.22±0.13	0.46 ± 0.12*		

Contractile responses to PGF were unaffected by TAM pretreatment but responses to PDB were greatly reduced. This was not dose-related but appeared to increase with duration of treatment. Thus chronic effects of TAM differed from acute actions observed in Group 1; further experiments using TAM for longer periods are necessary to confirm this. However, since chronic administration of TAM appeared to selectively relax contractions elicited by PKC activation, it seems unlikely that general vasorelaxant actions are involved in reducing risks of myocardial infarction during tamoxifen treatment.

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