TUESDAY, APRIL 27, 1982
AM
DRUG EFFECTS ON BLOOD VESSELS
8:30-10:00

MECHANISM OF OPIATE MEDIATED SYSTEMIC AND CORONARY VASOCONSTRICTION

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Administration of the Opiate fentanyl (F) 1.3 ug/kg into the lateral cerebral ventricle (i.c.) of conscious dogs causes an increase in systemic (SVR) and coronary vascular resistance (CVR). In 10 animals heart rate (HR) beats/min; aortic pressure (MAP) mm Hg; left atrial pressure (LAP) mm Hg; cardiac output (CO) ml/kg/min left circumflex coronary blood flow (CBF) ml/min were measured along with plasma arginine vasopression (AVP) pg/ml during control (C) and 3-5 min after F i.c. Values are mean ± of standard error(SEM).

	HR	AP	LAP	CO	SVR	CBF	CVR	AVP
C	91	88	5	107	0.028	31	2.8	4.69
SEM	± 9	±3	±1	±10	±0.002	±3	±0.3	±1.19
F	57*	117***	13**	57***	0.084**	19***	6.1***	77.45***
SEM	±3	±6	±5	±7	±0.018	±4	±0.7	±30.19

*p 0.05 **p .005 ***p .001

Naloxone (N) and the competitive AVP antagonist-D $(CH_2)_5$ Tyr (Me) AVP (AAVP) were studied in 6 conscious dogs. After N 0.10 mg/kg IV, F i.c. failed to significantly increase SVR, CVR and AVP.

	SVR	CVR	AVP
C	0.030	3.0	5.05
N	0.032	3.1	6.27
F	0.027	2.6	5.90

AAVP 20 ug/kg IV (n=6) prevented an increase in SVR and CVR despite an increase in AVP from 5.0 to 329 after F i.c. Thus, opiate mediated increases in SVR and CVR are due to AVP release. This mechanism may play a role in certain forms of hypertension and myocardial ischemia.

CONTRACTILE ACTIONS OF RACEMIC AND d-PROPRANOLOL ON ISOLATED CANINE MESENTERIC AND CORONARY ARTERIES

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This investigation was undertaken to determine whether propranolol (P) exerts a direct vasoconstrictor action which contributes to the increased systemic and regional vascular resistance observed after its acute administration. Helically cut strips of canine mesenteric (M) and coronary (C) arteries were exposed to cumulative concentrations of racemic P, d-P, metoprolol, and sotalol. Racemic and d-P were equipotent in eliciting concentration-related increments in tension in the M ($3x10^{-6}$M to $3x10^{-5}$M) and C ($3x10^{-7}$M to $3x10^{-5}$M) arterial strips. Metoprolol and sotalol did not cause contractions in concentrations up to 10^{-4}M. Phenoxybenzamine, 10^{-6}M, did not alter the contractile responses elicited by racemic and d-P. Upon exposure of M strips to calcium-free media or 10^{-6}M verapamil, the contractile responses to P ($3x10^{-5}$M) and KCl (30 mM) were markedly reduced (not significantly different), while norepinephrine (10^{-6}, 10^{-5}M)-induced responses were inhibited to a significantly lesser degree. In C arteries exposed to calcium-free media or 10^{-6}M verapamil, the responses to P, KCl, and methoxamine (10^{-5}M) were all extensively decreased (not significantly different). These results indicate that P exerts a direct contractile effect on canine M and C arteries. This effect of P is unrelated to its beta-adrenergic blocking activity and is not mediated through action on alpha-adrenergic receptors. The P-induced contraction appears to be associated predominantly with an influx of calcium ions across the vascular smooth muscle-cell membrane.

KETANSERIN -- A SELECTIVE SEROTONERGIC BLOCKING AGENT IN VASCULAR SMOOTH MUSCLE

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The differentiation of monoaminergic receptors depends upon the availability of selective antagonists. Most agents antagonizing serotonin (5-HT) in vascular smooth muscle lack specificity and block other monoamines including α-agonists, histamine,and dopamine. The selectivity of Ketanserin (KS;R-41468) was tested in isolated rabbit aorta. Arterial ring preparations were mounted in a myograph for the recording of isometric tension, and equilibrated with oxygenated Krebs buffer containing propranolol (10^{-6} M) and inhibitors of monoamine uptake (10^{-5} M cocain; 10^{-6} M fluoxetine). Concentration-response experiments (n = 36) for 5-HT in the presence of varying KS concentrations revealed competitive antagonism. Schild plots showed an apparent dissociation constant (K_D) for KS of 3.10^{-9} M. KS did not attenuate contractions elicited by μM concentrations of histamine, norepinephrine, methoxamine, and phenylephrine. Cyproheptadine was effective in blocking 5-HT (K_D = $5{\cdot}10^{-9}$ M), but also blocked 10^{-6} M histamine with a 10^{-7} M concentration. Radioligand binding experiments with particulate fractions from rabbit aorta (40,000 x g minus 3000 x g pellet) using 5-HT (10^{-4} M) or cyproheptadine (10^{-5} M) as displacing agents were performed. K_D values were determined by the Scatchard method and showed values between 1 to $2{\cdot}10^{-9}$ M, in close agreement with the indirect pharmacological procedure. We conclude that Ketanserin is a potent and specific competitive antagonist of serotonin in rabbit aorta.

COMPARATIVE EFFECT OF VERAPAMIL AND NITROGLYCERIN ON COLLATERAL BLOOD FLOW IN THE DOG

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This study was undertaken to compare the effects of verapamil (V) and nitroglycerin (TNG) on the collateral blood flow to the central and border zones of ischemic myocardium. In 12 dogs the left main and left anterior descending (LAD) coronary arteries were separately cannulated and perfused from the carotid. The myocardium not perfused by the LAD was thus labelled with microspheres. The LAD was then occluded and the circumflex perfusion pressure kept constant using a servo-pump. V and TNG were infused at constant rates into the left main coronary artery to increase the monitored coronary blood flow by approximately 25-50%. The order of V and TNG administration were alternated. Regional myocardial blood flows,in ml/min/g, were measured with each intervention using microspheres and compared by analyses of variance. The LAD and left main arteries were injected with different colored gelatin and the central-ischemic, border and normal zones excised for counting. The flows in the normal tissue increased from 0.816 to 1.010 with TNG and to 1.232 with V. Tbe control flow in the central ischemic tissue was 0.091 and did not significantly increase with V (0.097) but did with TNG (0.142, $p < 0.001$). Flows in the border region increased from control 0.380 to 0.561 for V ($p < .025$). However, when these were corrected for interdigitation with normal tissue only TNG increased flow in this region. Thus TNG increases collateral blood flow in both central ischemic and border zone tissues. V does not increase flow to either of these regions. The mechanism of action of V in relief of angina is presumably not due to an increase in collateral blood flow.