The effect of large oral doses of vitamin C on the chronotropic action of isoprenaline in man

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It was found in dogs (Houston, Wilkens & Levy, 1976) that intraduodenal administration of isoprenaline together with vitamin C caused a much greater increase in the heart rate (HR) than was observed after administration of isoprenaline alone. No potentiating effect was detected when isoprenaline and the vitamin were injected intravenously. The purpose of this study was to investigate the influence of large oral doses of vitamin C on the positive chronotropic action of isoprenaline in man. Twenty patients (11 men and 9 women; mean age 47 years) participated in the study. Patients with signs or symptoms of renal or liver malfunction, heart disease, arterial hypertension or gastrointestinal disease were excluded from the group. Fasted overnight, the subjects took vitamin C and/or isoprenaline on three consecutive days, according to a Latin-square design. On one morning, after recording HR and blood pressure (BP) 30 mg of isoprenaline was given in a sustained action tablet (PROTERNOL®, Key Pharmaceuticals, Inc.), and HR as well as BP were recorded every ten minutes till the isoprenaline-induced tachycardia had worn off. On another day the patients took one gram vitamin C per os at 7.00, 8.00, 9.00, 10.00 and 11.00 h. At 9.00 they also received 30 mg of isoprenaline, and the parameters were recorded every tenth minute. On a third day at 7.00 h a bolus injection of 5 μg of isoprenaline was administered intravenously in 1 min, and HR and BP were measured every minute till the isoprenaline-induced circulatory changes had disappeared. The doses of 1 g of vitamin C were administered in each hour till 11.00 h, when the isoprenaline challenge had been repeated as before.

Resting HR was identical (72 ± 5; 71 ± 5 beat/min respectively) on both days with the oral administration of isoprenaline. Maximum HR increase was 16 ± 3 beat/min following isoprenaline alone while isoprenaline plus vitamin C produced a HR increase of 12 ± 4 beat/min. The difference is statistically not significant (NS). However, the area under the HR curve was significantly less in case of the concomitant administration of isoprenaline and vitamin C than in case of isoprenaline alone ($P < 0.01$). There was a positive chronotropic response of 26 ± 4 beat/min following the bolus injection of isoprenaline. The response was almost identical (25 ± 5 beat/min) after vitamin C pretreatment. There was no significant change in BP.

These data suggest that vitamin C in large oral doses is decreasing the chronotropic effect of the concomitantly administered isoprenaline in man.

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Antagonism by (+)-amphetamine of the inhibition of [^{3}H]-noradrenaline overflow obtained by alpha-adrenoceptor agonists or bretylium in the perfused cat spleen

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In the rabbit perfused heart (+)-amphetamine counteracts the block of adrenergic transmission induced by guanethidine and clonidine but not by tetracaine (Starke, Wagner & Schümann, 1972). The concentrations of amphetamine employed in these experiments increased by themselves the release of noradrenaline induced by nerve stimulation (Starke, *et al.*, 1972). Consequently, an algebraic sum of effects resulting from interactions at different receptor sites cannot be excluded. The aim of the present experiments was to reexamine and clarify the antagonism by amphetamine of the effects of alpha-adrenoceptor agonists on transmitter release induced by nerve stimulation.

The present experiments were carried out in the perfused cat spleen prelabelled with [^{3}H]-noradrenaline. The nerves were stimulated at 1 Hz during 5 min. In the controls the fraction of the total tissue radioactivity released per shock was $12.10 \pm 1.24 \times 10^{-5}$ during the first period of stimulation (S_1) and $12.17 \pm 1.04 \times 10^{-5}$ ($n = 4$) in S_2. When the results were expressed as the ratio obtained between two consecutive periods of nerve stimulation the value

S_2/S_1 was 1.02 ± 0.04, $n = 4$. Exposure to the neuronal blocking agent bretylium (10 μM) or to the alpha-adrenoceptor agonist, oxymetazoline (0.3 μM) before S_2 reduced the stimulation evoked overflow of the tritiated transmitter (S_2/S_1:0.49 ± 0.13, $n = 4$, $P < 0.001$ for bretylium and 0.50 ± 0.09, $n = 6$, $P < 0.001$ for oxymetazoline). The alpha adrenoceptor blocking agent, phentolamine (3.1 μM) which increases [^{3}H]-transmitter overflow by blocking presynaptic alpha adrenoceptors (Langer, 1974, 1977; Starke, 1977) antagonized the inhibition in [^{3}H]-transmitter overflow elicited by nerve stimulation in the presence of oxymetazoline (0.3 μM) but did not prevent the inhibition obtained in the presence of bretylium. These results indicate that the inhibition of neurotransmission by bretylium is not mediated through an effect on presynaptic alpha-adrenoceptors.

In the perfused cat spleen, exposure to amphetamine (either 1 μM or 3 μM) when added before S_2 failed to affect [^{3}H]-transmitter overflow (S_2/S_1:1.11 ± 0.08, $n = 29$ and 0.91 ± 0.08, $n = 11$ for 1 and 3 μM amphetamine respectively). Under these experimental conditions both concentrations of amphetamine antagonized the inhibition of [^{3}H]-transmitter overflow elicited by nerve stimulation in the presence of bretylium (10 μM) or oxymetazoline (0.3 μM). On the other hand amphetamine (1 μM), failed to antagonize the inhibition of neurotransmission induced by the dopamine receptor agonist, apomorphine (0.1 μM) and the muscarinic receptor agonist, carbachol (0.3 μM). The failure of amphetamine to antagonize the inhibition of neurotransmission mediated by the activation of presynaptic dopamine or muscarinic receptors excludes the possibility that these effects of amphetamine are of a non specific nature.

Inhibition of neuronal uptake with cocaine (29 μM) did not *per se* affect the stimulation evoked release of [^{3}H]-noradrenaline (S_2/S_1: 0.74 ± 0.10, $n = 4$). Cocaine (29 μM) like amphetamine (1 μM) antagonized the inhibition of neurotransmission induced by oxymetazoline but did not modify the magnitude of the inhibition induced by alpha methyl noradrenaline (0.1 μM). Imidazolines have been shown to possess partial agonist properties on presynaptic alpha adrenoceptors (Medgett, McCulloch & Rand, 1978), particularly when the concentration of noradrenaline in the synaptic gap is increased by changing the parameters of stimulation or as a consequence of inhibition of noradrenaline uptake.

It is concluded that amphetamine, in concentrations in which it does not *per se* affect the stimulation evoked release of noradrenaline antagonizes the inhibition of neurotransmission induced by the neurone blocking agent bretylium and by the alpha adrenoceptor agonist, oxymetazoline.

It is likely that the inhibition of neuronal uptake by increasing the noradrenaline concentration in the synaptic gap, antagonizes the decrease in neurotransmission induced by oxymetazoline, but does not modify the inhibition obtained with alpha methyl noradrenaline. The former is an imidazoline with partial agonist properties while the latter is a catecholamine. Therefore, the estimations of relative order of potencies of imidazolines on presynaptic receptors under experimental conditions in which uptake inhibitors were used may need extensive reevaluation.

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